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EXPERIMENTAL STUDIES ON HEADACHE

FURTHER ANALYSIS OF THE MECHANISM OF HEADACHE IN MIGRAINE, HYPERTENSION AND FEVER

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Earlier studies have indicated that the dilatation and distention of cranial arteries form the basis of the headache produced by a variety of factors.[1] The purpose of this communication is to analyze further the mechanism of such headache and to ascertain which cranial arteries are responsible for the headache in each instance.

MIGRAINE HEADACHE

EFFECT OF VARIOUS AGENTS

It was shown [1b] that the termination of attacks of migraine headache by ergotamine tartrate regularly paralleled the decrease in amplitude of pulsations of the cranial arteries, chiefly certain branches of the external carotid artery. Pressure over the common carotid artery on the side of the headache reduced the severity of the attack during the pressure. The amelioration was associated with decreased amplitude of pulsations of the temporal artery. Conversely, the distention of the walls of the cranial arteries, for example, experimental distention of the temporal and the middle meningeal arteries, caused pain in the temporal region.[2]

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1. (*a*) Clark, D.; Hough, H. B., and Wolff, H. G.: Experimental Studies on Headache: Observations on Histamine Headache, A. Research Nerv. & Ment. Dis., Proc. (1934) **15**:417, 1935; Arch. Neurol. & Psychiat. **35**:1054 (May) 1936. (*b*) Graham, J. R., and Wolff, H. G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:638, 1939; Arch. Neurol. & Psychiat. **39**:737 (April) 1938. (*c*) Wolff, H. G.: Headache and Cranial Arteries, abstracted, Tr. A. Am. Physicians **53**:193, 1938.

2. (*a*) Graham and Wolff.[1b] (*b*) Wolff.[1c] (*c*) Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance in Headache, Arch. Surg. **41**:813 (Oct.) 1940.

Epinephrine decreased the intensity of the headache during a brief period of decreased amplitude of pulsations, but as the amplitude returned to the original level the headache became as severe as before the administration of the drug.

That ergotamine tartrate has no analgesic action in itself has been demonstrated.[3] Administration of full therapeutic doses does not affect the pain threshold. Also, it has been shown [4] that ergotamine tartrate does not diminish the intensity of nonmigrainous headache.

It may be concluded [1b] that the pain associated with the migraine attack is caused by the dilatation and distention of cranial arterial walls and that the therapeutic effect of ergotamine tartrate depends on its ability to produce prolonged and powerful vasoconstriction.

If this conclusion is valid it must be true that any agent producing decrease in the amplitude of pulsations of the cranial arteries comparable in magnitude and duration to the effect of ergotamine tartrate will produce comparable effects in ending headache. Studies have therefore been made with other vasoconstrictor substances, namely, ergonovine (an isomeric alkaloid of ergot), caffeine, benzedrine, ephedrine and pitressin. The contrasting influence on the headache of the vasodilator agents histamine and amyl nitrite also were further studied. Finally, the cranial arteries during the headache-alleviating action of codeine, acetylsalicylic acid and acetophenetidin were investigated. The experiments described were performed when the prodromes of the migraine attack had been supplanted by headache; the results, therefore, have no bearing on the preheadache phenomena.

Method.—Pulsations of the temporal branch of the external carotid artery were recorded by means of a tambour placed on that artery where it could be palpated under the skin.[1a] The tambour was connected to a Frank capsule by means of a thick rubber tube. A beam of light from a slit lamp was thrown on a mirror on the thin rubber diaphragm and was reflected to and recorded on moving bromide paper. Any pulsation transmitted to this air system by the artery caused the mirror to deflect the beam of light through an arc, the length of which was proportional to the force of the impulse. Readings of blood pressure were made at frequent intervals.

Changes in the intensity of the headache were estimated by the patient and recorded in percentages with the understanding that 100 per cent represented the headache at the time of starting the experiment. At least three records of the amplitude of pulsations of the artery were made at intervals of several minutes during the headache to obtain suitable measurements as controls. At the time of

3. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies on Pain: Measurement of the Effect on the Pain Threshold of Acetylsalicylic Acid, Acetanilid, Acetophenetidin, Aminopyrine, Ethyl Alcohol, Trichlorethylene, a Barbiturate, Ergotamine Tartrate, and Caffeine; an Analysis of Their Relation to the Pain Experience, to be published.

4. Lennox, W. G.; von Storch, T. J. C., and Solomon, P.: Effect of Ergotamine Tartrate on Non-Migrainous Headache, Am. J. M. Sc. **192**:57, 1936.

each measurement the patient was asked to estimate the intensity of his headache; simultaneously blood pressure readings were taken.

It should be emphasized that the temporal artery is not the only cranial artery responsible for the head pain. Because of its technical availability, it has been used as a representative branch of the external carotid artery.

Agents Decreasing the Amplitude of Pulsations of Cranial Arteries.—Ergonovine: To 5 patients 0.2 mg. of ergonovine hydracrylate was administered intravenously. In 2 of these patients the headache was abolished; in 2 it was unaffected, and in 1 the intensity was diminished. When the headache was abolished or diminished, the decrease in amplitude of pulsations of the temporal artery closely paralleled the decrease in the severity of the headache. When the headache was not terminated, the amplitude of pulsations was found to have changed relatively little.

The usual reduction in the amplitude of pulsations of the cranial arteries with the abolition of the migraine headache by means of ergotamine tartrate was found[1b] to be approximately 50 per cent. In the 2 patients whose headache ended after the administration of ergonovine, the decline of amplitude of pulsations of the temporal artery was 35 and 50 per cent, respectively. Of the 2 whose headache was not ended, there were an increase of 8 per cent in amplitude of pulsations in 1, and a decrease of 25 per cent in the other. In the fifth subject, the severity of whose headache was reduced an estimated 75 per cent, the amplitude of pulsations decreased 28 per cent.

In the 2 patients whose headache was not ameliorated by ergonovine, the subsequent intravenous administration of 0.5 mg. of ergotamine tartrate was followed by a decrease of 40 and 53 per cent respectively in the amplitude of pulsations, with concurrent abolition of the headache.

The effect of ergonovine in ending headache was variable in these patients, as in those reported elsewhere,[5] but the variability here recorded could be correlated with the capacity of the drug in the individual patient to effect a reduction in the amplitude of pulsations of the cranial arteries to a degree comparable with that of the result produced by ergotamine tartrate.

It may be that ergonovine acted more slowly than ergotamine tartrate and that in the case of subjects not relieved by ergonovine, insufficient time was allowed for it to become effective before the ergotamine tartrate was given. Nevertheless, the principle stands that the headache-ending effect was dependent on a decrease in the amplitude of pulsations.

Caffeine with Sodium Benzoate: To 2 patients 0.5 Gm. of caffeine with sodium benzoate was given intravenously. There was an increase of 10 and 22 per cent, respectively, in the amplitude of pulsations of the temporal artery, and both patients complained of increased headache. Subsequent administration of ergotamine tartrate reduced the amplitude of pulsations to 33 and 46 per cent, respectively, of the original level, with abolition of the headache. Hot strong coffee, administered by mouth to 2 patients, effected moderate reduction both in the amplitude of pulsations of the temporal artery and in the severity of the headache.

5. Lennox, W. G.: Ergonovine Versus Ergotamine as Terminator of Migraine Headaches, Am. J. M. Sc. **195**:458, 1938.

These results are consistent with the known effects of caffeine,[6] for when administered intravenously it may act as a vasodilator, whereas when given orally, with a slower rate of absorption, it may act as a vasoconstrictor.

Benzedrine Sulfate: Three patients each received 10 mg. of benzedrine sulfate intramuscularly. In 2 there was a decrease of 2 and 10 per cent, respectively, in the amplitude of pulsations of the temporal artery; the headache was not ameliorated until the amplitude of pulsations decreased 33 and 28 per cent, respectively, after the administration of ergotamine tartrate. In the third patient, however, benzedrine sulfate produced a decrease of 37 per cent in the amplitude of pulsations, with prompt abolition of the headache. The patients who received benzedrine complained of muscular tension, tremor and palpitation.

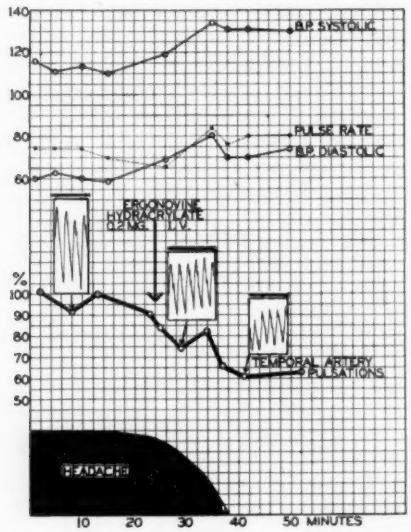

Chart 1.—Relation between the amplitude of pulsations of the temporal artery and the intensity of migraine headache after the administration of ergonovine hydracrylate. The decrease in the amplitude of pulsations following injection of ergonovine paralleled the decrease in the intensity of the headache. Representative sections of the photographic record are inserted. The average amplitude of pulsations for any given minute before or after administration of ergonovine was ascertained by measuring the individual pulsations from the photographic record. In this record and in those in the accompanying figures the initial or control amplitude was taken as 100 per cent. The interrupted line above the photographic records represents intervals of one second.

Ephedrine Sulfate: One patient was given very slowly 0.013 Gm. of ephedrine sulfate intravenously. In five minutes the amplitude of pulsations had decreased 32 per cent, with termination of the headache. Immediately after the injection

6. Sollmann, T.: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936.

there was a sharp rise in pulse rate and blood pressure, and the patient complained of tension, lightheadedness and palpitation.

Pitressin: Two patients received 20 pressor units of pitressin intramuscularly. In 1 patient, termination of the headache paralleled the decrease of 70 per cent in the amplitude of pulsations; in the other, the amplitude of pulsations decreased 46 per cent with persistence of a remnant of the original headache. Both patients complained of lightheadedness and abdominal pain. In the patient whose headache was incompletely relieved, the headache returned in two hours to its original level.

The average decrease in the amplitude of pulsations of the temporal artery in patients whose migraine headache was lessened or abolished by agents other than ergotamine tartrate was 42 per cent. In the

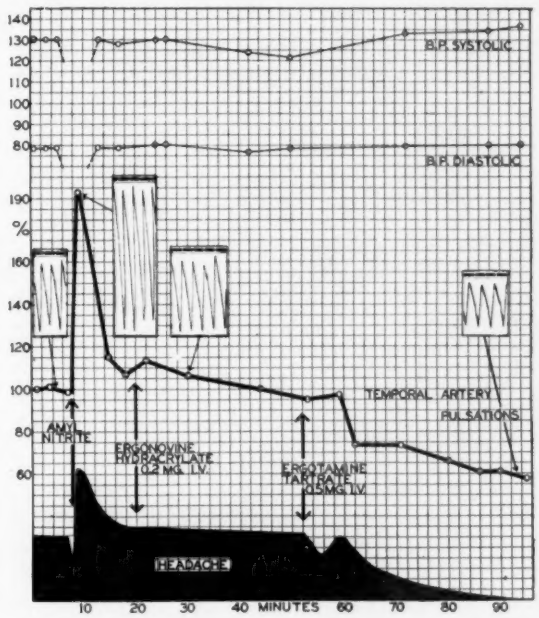

Chart 2.—Relation of the amplitude of pulsations of the temporal artery to migraine headache. Administration of amyl nitrite was followed by a momentary decrease in the intensity of the headache. This was followed by a sharp increase in the amplitude of pulsations and a parallel increase in the severity of the headache. Subsequent administration of ergonovine resulted in a slight decrease in the amplitude of pulsations with but slight amelioration of the headache. On administration of ergotamine tartrate, there was decrease in the amplitude of pulsations and the headache was abolished.

patients whose headache was not lessened, the change in amplitude of pulsations varied from an increase of 22 per cent to a decrease of 25 per cent; on subsequent administration of ergotamine tartrate during the same attacks, the average decrease in the amplitude of pulsations of

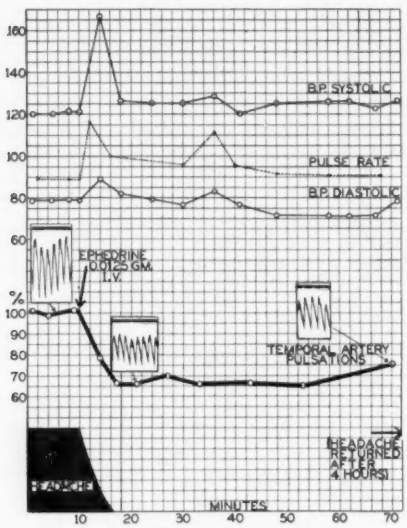

Chart 3.—Relation of the amplitude of pulsations of the temporal artery to the intensity of the migraine headache after very slow intravenous administration of ephedrine sulfate. With a sudden decrease in the amplitude of pulsations of the temporal artery, the headache was abolished.

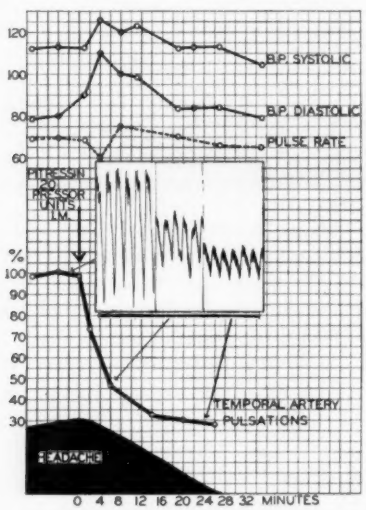

Chart 4.—Relation of the pulsations of the temporal artery to the intensity of the migraine headache following administration of pitressin. The decline in amplitude of pulsations of the temporal artery paralleled the decrease in severity of the headache.

the temporal artery was 43 per cent, a figure comparable with the 50 per cent decrease reported previously.[1b] Thus, it is clear that agents other than ergotamine tartrate lessened or abolished the headache when, and only when, they reduced the amplitude of pulsations to a degree comparable with that produced by the ergotamine tartrate. Of the agents studied thus far, ergotamine tartrate had the most constant and lasting effect in ending headache and, despite the frequently occurring nausea and vomiting, had fewer objectionable side effects.

Agents Increasing the Amplitude of Pulsations of Cranial Arteries.—If the effectiveness of ergotamine tartrate and other agents in terminating migraine headache is due to their ability to produce prolonged and powerful vasoconstriction, then vasodilator agents such as amyl nitrite and histamine phosphate should increase the severity of the migraine headache. This view is supported by the following experimental data.

Amyl Nitrite and Histamine Phosphate: The headache-inducing effect of amyl nitrite was first studied in 5 subjects not having a migraine attack. The inhalation of amyl nitrite produced a prompt fall both in systolic and in diastolic blood pressure. Headache was experienced when there had been a return of the blood pressure toward the previous level, with increase in the amplitude of pulsations of the cranial arteries. The headache subsequently disappeared, with return of the pulsations to the initial level. The mechanism of the headache is therefore exactly like that described[7] for the headache induced by histamine.

It has been shown[8] that the headache following injection of histamine is not prevented or reduced in intensity by the previous administration of ergotamine tartrate. Similarly, ergonovine and ergotamine (2 patients) had no effect in preventing or reducing headache caused by amyl nitrite.

Inhalations of amyl nitrite were given to 2 patients with migraine headache. After a brief initial decline in the intensity of the headache and in the amplitude of pulsations, there were marked increase in the amplitude of pulsations of the temporal artery and increase in the intensity of the headache attack (chart 2) in both patients. The intravenous administration of histamine phosphate, 0.1 mg., to 2 subjects resulted in a brief initial decline in intensity of headache and in amplitude of pulsations, followed by an increase in amplitude of pulsations of the temporal artery of several hundred per cent, and an almost unbearable increase in the severity of the headache.

The interpretation of these experiments must include the consideration of two factors: first, the intensifying effect on the migraine headache of increasing the relaxation of the branches (scalp and dural) of the external carotid artery; second, the additional effect of relaxing the

7. (*a*) Pickering, G. W., and Hess, W.: Observations on Mechanisms of Headache Produced by Histamine, Clin. Sc. **1**:77, 1933. (*b*) Clark, Hough and Wolff.[1a]

8. Lennox, von Storch and Solomon.[4] Graham and Wolff.[1b]

pial and cerebral arteries,[9] which in itself would induce headache. The latter effect might cause a headache surpassing in intensity the effect of further dilatation of the branches of the external carotid artery.[10]

Codeine, Acetylsalicylic Acid and Acetophenetidin.—Studies were made on the effect of the administration of codeine, acetylsalicylic acid and acetophenetidin on the migraine headache.

Four patients received 0.06 Gm. of codeine phosphate subcutaneously. The headache attacks were ended in 2 patients and were not appreciably affected in the other 2. In no instance was there any significant alteration in the amplitude of pulsations of the temporal artery. In the patients whose attacks were not ended by codeine, the subsequent administration of ergotamine tartrate resulted in the abolition of the headache, with parallel decrease in the amplitude of pulsations of the temporal artery.

When acetylsalicylic acid (3 subjects) and acetophenetidin (3 subjects), each in doses of 0.3 Gm., ended or ameliorated the headache, neither affected the amplitude of pulsations of the temporal artery.

From these observations the following inferences may be drawn: The mere abolition of pain in the head does not in itself bring about a decrease in the amplitude of pulsations of the cranial arteries, since codeine, acetylsalicylic acid and acetophenetidin terminate headache without influencing the amplitude of these pulsations. Therefore the reduction in the amplitude of pulsations brought about by ergotamine tartrate cannot be regarded as a fortuitous event attendant on the relief of pain in the head. It is evident that in terminating headache these drugs operate through a different mechanism than that for ergotamine tartrate.

The action of codeine, acetylsalicylic acid and acetophenetidin has been studied intensively elsewhere.[11] It has been found that the pain threshold is raised appreciably (30 to 55 per cent). With codeine, other effects, such as apathy, lethargy and freedom from tension, occur. The

9. (*a*) Leake, J. P.; Loevenhart, A. S., and Muehlberger, C. W.: Dilatation of Cerebral Blood Vessels as a Factor in Headache, J. A. M. A. **88**:1076 (April 2) 1927. (*b*) Hitz, J. B., and Kammer, A. G.: The Effects of Stimulation of Cerebral Blood Vessels, Thesis, University of Wisconsin Graduate School, 1926; cited by Leake, Loevenhart and Muehlberger.[9a] (*c*) Wolff, H. G.: The Cerebral Circulation: XIc. The Action of Amyl Nitrite, Arch. Neurol. & Psychiat. **22**:695 (Oct.) 1929.

10. Schumacher, G. A., and Wolff, H. G.: Experimental Studies in Headache: A. Contrast of Histamine Headache with the Headache of Migraine and That Associated with Hypertension. B. Contrasting Vascular Mechanisms in Preheadache and Headache Phenomena of Migraine, to be published.

11. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies in Pain Sensation: II. The Quantitative Analysis of the Action of Analgesics, Am. J. Physiol. **126**:656, 1939; Studies on Pain: Measurement of the Effect of Morphine, Codeine, and Other Opiates on the Pain Threshold and an Analysis of Their Relation to the Pain Experience, to be published; footnote 3.

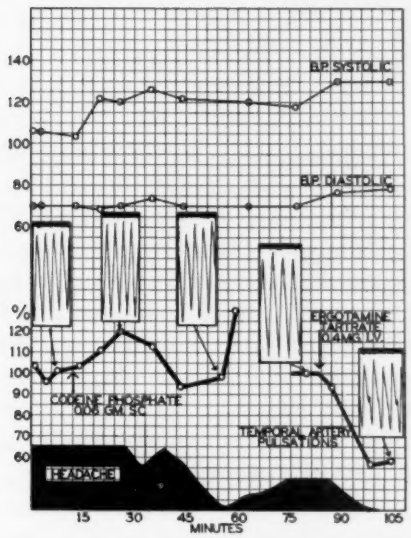

Chart 5.—Relation between the amplitude of pulsations of the temporal artery and the state of the migraine headache after administration of codeine phosphate and of ergotamine tartrate. After the administration of codeine there was a decrease in the intensity of the headache but no change in the amplitude of pulsations. After the administration of ergotamine tartrate, however, the amplitude of pulsations of the temporal artery decreased to 55 per cent of the original level with abolition of the headache.

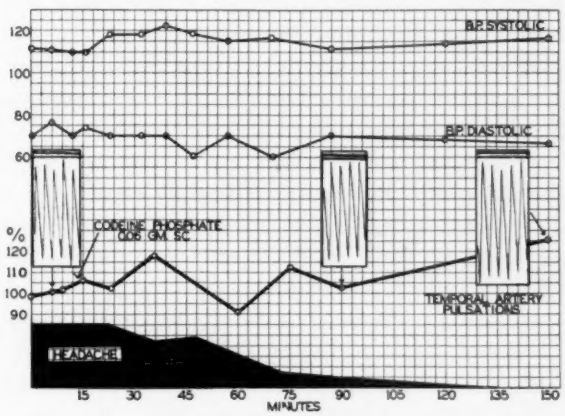

Chart 6.—Relation between the amplitude of pulsations of the temporal artery and the intensity of the migraine headache, which was ultimately terminated by codeine phosphate. Despite the abolition of the headache, there was no decrease in amplitude of pulsations of the temporal artery.

action of these drugs in alleviation of headache is thus not dependent on elimination of the source of pain, as is the case with ergotamine tartrate.

CRANIAL ARTERIES INVOLVED AND DISTRIBUTION OF HEADACHE IN MIGRAINE

It was pointed out previously [1b] that attacks of migraine headache failed to recur after ligation of the middle meningeal artery. Similar results were obtained with 2 additional subjects. The beneficial effect lasted no longer than six months. Recent experiments [2c] with the middle meningeal artery have demonstrated that distention as well as faradic stimulation and traction caused severe pain in the temporal region or behind the eye. Since pain is common in this region during migraine headache, it is possible that the middle meningeal artery contributes to the attack of migraine headache.[2c]

The role of the pial and cerebral arteries in the migraine headache needs further definition. It should be recalled that faradic stimulation of the proximal few centimeters of the anterior, middle and posterior cerebral arteries and the first few centimeters of the intracranial portion of the internal carotid artery causes pain within, behind or over the homolateral eye.[2c] Furthermore, stimulation of the vertebral and basilar arteries and the proximal portions of their branches causes pain in the occipital and the suboccipital region. These areas are commonly involved in migraine attacks. The evidence from persons who have migraine headache that headache induced by histamine resembles the most intense migraine headache also suggests that the larger arteries of the base of the brain and their immediate branches may be implicated in some patients during severe migraine headache.

On the other hand, there is considerable evidence against this view. If the headache were due primarily to dilatation of the dural and cerebral arteries, raising the cerebrospinal fluid pressure would dampen the pulsations of these vessels and the headache would diminish, as in the case of the headache induced by histamine. Since not even the worst attacks of migraine headache are reduced in intensity by raising the cerebrospinal fluid pressure as high as 800 mm. of water by means of a manometer system attached to a needle in the lumbar sac, it is indicated that the pial and cerebral arteries are not the major contributors to the pain.[10]

The internal and the external carotid artery and the vertebral arteries have branches both in the subcutaneous tissue and in the meninges. The branches of the external carotid artery predominate numerically both superficially and on the dura. On the other hand, the anterior meningeal

artery arises from branches of the internal carotid artery, as do the superficial frontal and the supraorbital artery. Since the area supplied by the latter structures is commonly involved in migraine headaches, branches of the internal carotid artery may contribute to the pain. It is obvious, therefore, that it would be arbitrary to contrast these arteries too sharply.

Although most attacks of migraine headache are limited to the temporal, the frontal or the occipital region, some patients have pain elsewhere. In the face, below the eye and behind and below the zygoma, severe throbbing pain, which seems to emanate from the back teeth of the upper jaw, occasionally occurs. Another variant is facial pain, which spreads behind the angle of the jaw, down the neck and into the shoulder. The latter aching sensations are sometimes associated with awareness of unusual throbbing in the neck.

The pains described can and probably do result from dilatation and distention of the extracranial portion of the middle meningeal artery, between its origin and the point of entrance into the skull, the internal maxillary artery and the trunks of the external and the common carotid artery. It has been shown that the latter structures are sensitive to pain, and the sites in which pain is felt are the face, neck and shoulder.[12]

HEADACHE ASSOCIATED WITH HYPERTENSION

Studies made of the headache associated with hypertension have revealed that essentially the same mechanism is operative in producing this pain as in producing the migraine headache.[1c] It is to be emphasized that this statement applies not to the so-called hypertensive encephalopathy of Fishberg,[13] or "hypertensive crisis," but rather to the frequent, severe and often incapacitating headaches suffered by hypertensive patients who may otherwise be free of symptoms. The term "hypertensive headache" is misleading, since it implies that the frequency and severity of the headache are directly related to the level of the blood pressure.

As a matter of fact, it is a common clinical observation that the headache associated with hypertension yields to rest in bed or other methods of relaxation without a material change in the blood pressure level. A typical example is the course observed in the following case:

J. R., a man aged 50, was seen for the first time in June 1938. He complained of frequently recurring severe headaches of almost three years' duration. During the previous three months the headaches had gradually become almost constant and

12. Fay, T.: Mechanisms of Headache, Tr. Am. Neurol. A. **62**:74, 1936.

13. Fishberg, A.: Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

incapacitating; the blood pressure was 210 systolic and 120 diastolic. A month later, July 1938, his headache had become less severe; the blood pressure was 225 systolic and 134 diastolic. One year later, June 1939, he had had no headache in more than six months; the blood pressure was 240 systolic and 140 diastolic.

Almost all the patients with hypertension and associated headaches in this series had "headaches" for many years. In numerous instances the headache was known to precede the onset of the hypertension and changed in some patients only in intensity with the rise in blood pressure.

Observations.—For three days, hourly determinations of the systolic and diastolic blood pressures were made on 4 patients suffering from headache associated with hypertension. No relation between either the incidence or the severity of the headache and the immediate level of the systolic or the diastolic blood pressure could be demonstrated. The headache might be present or absent when the pressure was high or moderate, or indeed even relatively low (chart 7).

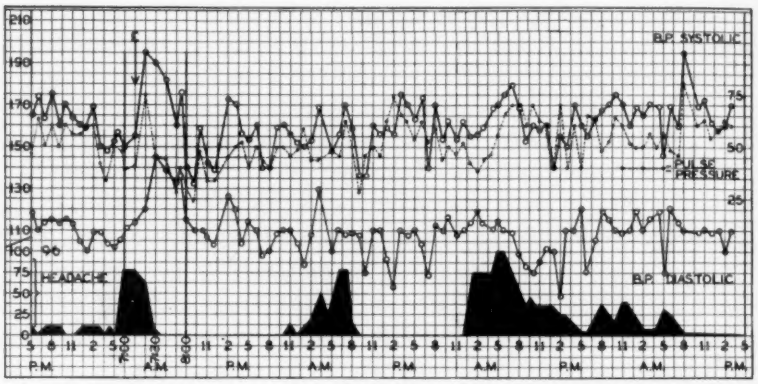

Chart 7.—Relation of blood pressure to headache in a patient with hypertension and associated headache. The fluctuations of the blood pressure and the incidence and severity of the headache vary independently. Thus, headache occurred with a blood pressure of 140 systolic and 75 diastolic on one occasion, whereas headache disappeared as the blood pressure rose from 145 systolic and 90 diastolic to 195 systolic and 110 diastolic at another time. At *E*, to the left of the chart, is shown the record of a headache terminated by ergotamine tartrate (chart 8).

Digital compression of the common carotid or the temporal artery resulted in decrease in the intensity of the headache on that side. When the effect of ergotamine tartrate on the headache of hypertension was tested (in the manner employed in the study of migraine headache), it was found that, despite sharp rises in blood pressure due to the ergotamine, there was a decrease in the severity of the headache, which paralleled the decrease in the amplitude of pulsations of extracranial arteries (chart 8). On the other hand, the administration of amyl nitrite or histamine caused the headache to increase in intensity during the period of increased amplitude of pulsations. In other words, factors that constricted the cranial arteries diminished, and those that dilated the cranial arteries increased, the intensity of the headache associated with hypertension.

During the headache the pressure of the cerebrospinal fluid was not unusual (from 80 to 170 mm. of water) and there was no increase in the amplitude of pulsations of intracranial arteries. Moreover, the amplitude of pulsations of these arteries did not become less as the headache diminished in intensity.

The effect of increasing the pressure of the cerebrospinal fluid was tested on the headache associated with hypertension. If, as in the case of histamine headache, increasing the cerebrospinal fluid pressure reduced the intensity of the headache, presumably by dampening the effect of cardiac systole on the intracranial arteries, a similar mechanism for the headache of hypertension could be postulated. No such effect was observed. Increasing the cerebrospinal fluid pressure as high as 750 mm. of water by means of a manometer attached to a needle in the lumbar subarachnoid space did not diminish the intensity of the headache.[10]

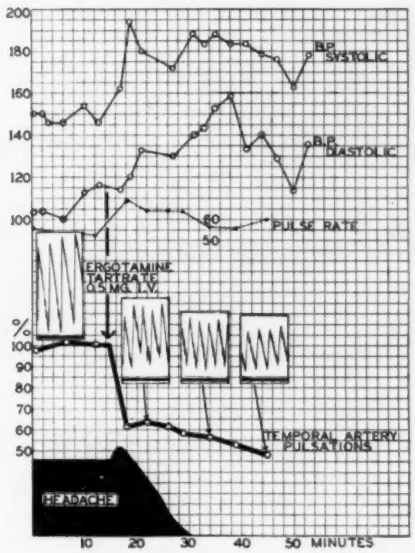

Chart 8.—Effect of ergotamine tartrate on headache associated with hypertension. The decrease in the intensity of the headache paralleled the decrease in amplitude of pulsations of the temporal artery. The fact that the headache is not causally dependent on the immediate level of the blood pressure is demonstrated here, for the blood pressure actually rose precipitously as the headache was abolished.

Further evidence that the dural and superficial branches of the external carotid artery contribute significantly to the headache of hypertension was furnished by the following intensive study (chart 9):

S. M., a man aged 48, with hypertension, had had incapacitating headache every morning, chiefly on the right side, for over a year. After the intensity and frequency of the headache had been recorded for a year, the right middle meningeal artery was ligated. After this procedure the daily headache on the side of the operation diminished somewhat in intensity. About a month later the right

temporal artery, carefully avoided in the first operation, was ligated. This procedure was followed by almost complete freedom from headache on the right side. Less intense headaches, though present before, were now more troublesome over the left eye and temple. Hence, about a month later, the left temporal artery was similarly ligated. During the subsequent three months no headache was experienced in either the right or the left temporal region. Such headache as occurred, which was approximately one third as intense as previously, was now localized in the region immediately over both eyes and in the midline. Throughout these procedures the levels of the systolic and the diastolic pressure did not vary appreciably, and such changes as took place bore no relation to the headache. Within four months, however, the incidence and severity of the headache returned toward previous levels.

High intracranial pressure has no part in the headache, since the cerebrospinal fluid pressure was shown to be normal during an attack.

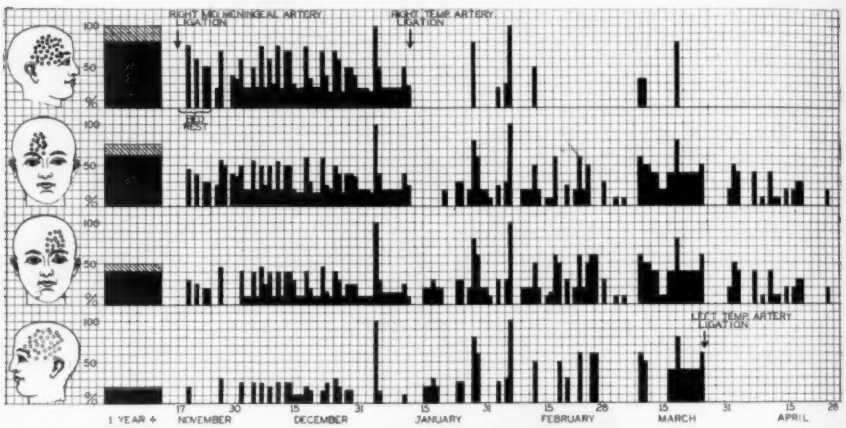

Chart 9.—Record of patient S. M., with hypertension and associated headache. Diagrams of the head illustrate the distribution of the headache. Pain was chiefly on the right, as indicated by the black dots. The solid black dots indicate the area of most intense headache. The solid black areas immediately to the right of the diagrams of the head, schematically represent the intensity of the headache for one year. The thin black columns indicate the intensity of the headache during the experimental period. After ligation of the right middle meningeal artery the headache on the right side was somewhat decreased in intensity. After ligation of the right temporal artery there was almost complete freedom from headache on the right side. Later, ligation of the left temporal artery similarly caused freedom from headache in the left temporal area. Headache remained in the frontal region. The level of the systolic and the diastolic blood pressure did not vary appreciably. Four months later the headaches returned.

The following facts indicate that the pial and cerebral arteries are not the prime contributors to the headache and that the headache associated with hypertension, like that of migraine, arises chiefly from the dilatation and distention of certain branches of the external carotid artery: 1. The

headache was not relieved by increasing the cerebrospinal fluid pressure. 2. There was no increase in the amplitude of pulsations of the intracranial arteries during the headache, and the amplitude of pulsations of these arteries did not become less as the headache diminished in intensity. 3. Ergotamine tartrate, which in the head acts chiefly on the branches of the external carotid artery, reduced the intensity of headache. 4. Manual pressure on the temporal, frontal, supraorbital, postauricular or occipital artery decreased or abolished the headache. 5. Ligation of the middle meningeal or the temporal artery, especially the latter, decreased the intensity of the headache for some months.

Janeway [14] made the following statement:

> A surprisingly large number of these [hypertensive] patients have been subject to migraine throughout life. . . . The headache is one which appears on awakening or wakes the patient in the early morning hours, has its greatest intensity before arising and passes away either immediately after breakfast or during the course of the morning to reappear in the same manner day after day for considerable periods. The intensity of the pain and its location have varied somewhat, the most severe being similar to bad migraine, and in a few cases it is attended by nausea and vomiting.

A further similarity of the headache associated with hypertension to that of migraine is suggested by a consideration of the location, quality and outstanding features of the headaches in Robey's [15] series of patients with hypertension. Thus, most of the patients had frontal, orbital, frontotemporal or temporal headache. The next most common site was the occiput, at which headache occurred one half as frequently as at the former sites. Generalized headache occurred about one fifth as frequently as did frontotemporal headache and half as frequently as occipital. Unilateral headache occurred in about 10 per cent of the patients. The headaches were commonly throbbing, and were worse in the morning.

That the hypertension does not bear a direct relation to headache associated with it is further supported by the data of Robey.[15] He found among 448 patients with hypertension, 218 who never had headache; in short, half the patients with hypertension had no headache whatever. Also, in a group of 303 outpatients with hypertension, 50 had headaches as a chief or major symptom, but these persons had practically the same level of systolic and diastolic blood pressure and of pulse pressure as did 150 patients who never had headaches.

The fact that the high level of blood pressure among hypertensive subjects is not a sufficient condition for headache does not justify the

14. Janeway, T. C.: A Clinical Study of Hypertensive Cardio-Vascular Disease, Arch. Int. Med. **12**:755 (Dec.) 1913.

15. Robey, W. H.: Headache, Philadelphia, J. B. Lippincott Company, 1931.

assumption that these phenomena are unrelated. Indeed, this, too, would be contradicted by the facts of common experience, since some persons with hypertension never had headache until the hypertension became established. It seems reasonable to postulate that a cranial artery only slightly relaxed for whatever reason would not distend as much, and possibly not to the point of producing pain, if the blood pressure were low. If, however, the sustained level were raised, distention would be greater and therefore pain might readily follow. In other words, a degree of change in the contractile state of the arterial wall, compatible with comfort when blood pressure is average, would be associated with pain when the blood pressure is elevated.

This conception is supported by analogy with experimental evidence on histamine headache.[16] The headache and maximal distention of the cranial arteries occur not immediately after the injection of histamine, when the effect on the contractile state of these vessels is greatest, but some time later, when the blood pressure returns to its initial level. It is at this time that the walls of the cranial artery react to the mounting pressure and headache becomes associated with a level of blood pressure which is ordinarily accompanied by comfort. The relaxation of arterial walls is thus seen to be one necessary factor in the production of histamine headache, and the level of the blood pressure the other. The analogy to the circumstances in hypertension is close. During an average or normal contractile state of the arterial walls, distention does not occur and, correspondingly, there is no headache; but should this contractile state be impaired, as by stress, fatigue or other condition, distention and headache follow. In brief, high blood pressure is a necessary but not a sufficient condition for this type of headache. There is, therefore, a significant relation between headache associated with hypertension and the contractile state of the cranial arteries.

HEADACHE ASSOCIATED WITH FEVER

Septicemia and fever are commonly associated with headache. This headache is dull, deep and aching; it is generalized, and is made worse by bodily movement. The intensity of the headache is insignificantly modified by manual compression of the branches of the external carotid artery, and ergotamine tartrate has little or no effect, except possibly toward the end of the period of headache, when occasionally in a few subjects the drug hastens the termination of the pain. Since it has been observed that the fever induced by the intravenous administration of typhoid vaccine is frequently associated with headache or with sensations

16. (*a*) Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936. (*b*) Pickering and Hess.[7a] (*c*) Clark, Hough and Wolff.[1a]

of fulness in the head, the relation of the cranial arteries to the headache was experimentally investigated in observations on patients in the wards of the New York Hospital who were undergoing fever therapy for chorea or rheumatoid arthritis.

Method.—A tambour was placed on the temporal artery, and the pulsations were recorded as heretofore described.[1a] In addition, a needle was introduced into the lumbar sac and connected to a Frank capsule by means of a continuous column of physiologic solution of sodium chloride. Light from a slit lamp was focused on a small mirror attached to the capsule and was reflected to a camera containing moving bromide paper. The pulsations of the cerebrospinal fluid caused the light reflected from the capsule into the camera to be deflected through an arc proportional to the amplitude of pulsations. As the pulsations of the cerebrospinal fluid are reflections of the pulsations of the intracranial and intraspinal arteries, measurements of the amplitude of pulsations in the cerebrospinal fluid afford an accurate estimate of the amplitude of pulsations of these arteries. The pulsations of the temporal artery and of the cerebrospinal fluid were simultaneously recorded. After a suitable control period, during which records were made, an appropriate dose (25,000,000 to 1,000,000,000 bacteria per cubic centimeter) of typhoid vaccine was administered intravenously. If no chill or rise in temperature took place within sixty or ninety minutes, a second and smaller dose was given. Estimates of the state of the headache, determinations of the blood pressure and records of the pulsations of the cerebrospinal fluid and the temporal artery were made at frequent intervals throughout the procedure.

Results.—Twelve such experiments were performed. Because of the many hours of immobilization necessary for a complete record of the beginning and the end of the cycle of fever and the consequent discomfort to patients with arthritis, experiments completely satisfactory from a technical point of view were not obtained. However, the observations were adequate and consistent and permitted inferences.

Onset of a headache or a sensation of fulness in the head was found in all instances to follow increased amplitude of pulsations of the cerebrospinal fluid and of the temporal artery. Spontaneous lessening of the headache closely paralleled the decrease in amplitude of these pulsations, and as the amplitude of the pulsations again increased the headache became more severe. With the ultimate decline in amplitude of these pulsations the headache ended. The pressure of the cerebrospinal fluid was at all times within the usual physiologic limits.

Observations of the amplitudes of pulsations of the temporal artery and the cerebrospinal fluid showed that here, too, the spontaneous increase and decrease of the headache paralleled the amplitude of pulsations.

The similarity between the pyrexial and the histamine headaches was previously noted.[17] The amplitude of pulsations of the cerebrospinal fluid in headache induced by fever and by histamine was greatly increased, in contrast to that in migraine headache, in which there was no increase in amplitude. Pickering[17a] added the observation that

17. (*a*) Pickering, G. W.: Experimental Observations on Headache, Brit. M. J. **1**:907, 1939. (*b*) Wolff.[1c]

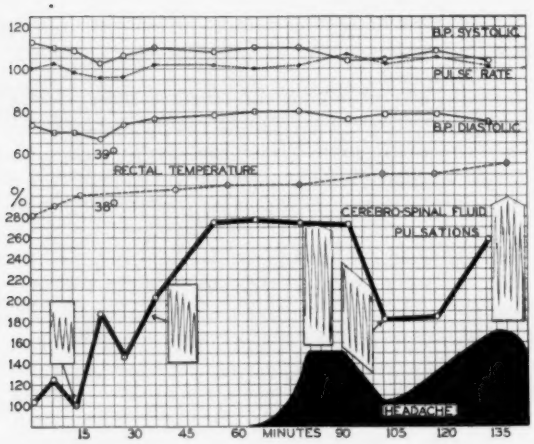

Chart 10.—Relation of the headache associated with intravenous injection of typhoid vaccine to the amplitude of pulsations of the cerebrospinal fluid. The onset, increase and decrease in intensity of the headache paralleled the amplitude of pulsations of the cerebrospinal fluid. A spontaneous remission in the severity of the headache paralleled the decrease in the amplitude of pulsations of the cerebrospinal fluid.

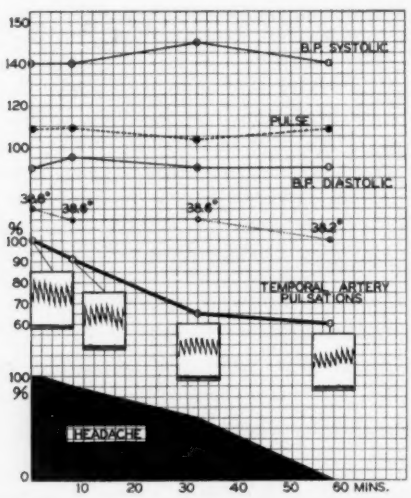

Chart 11.—Relation between the intensity of the headache and the amplitude of pulsations of the temporal artery in a case of headache associated with experimentally induced fever. The spontaneous amelioration in the intensity of the headache paralleled the decrease in amplitude of pulsations of the temporal artery.

increasing the cerebrospinal fluid pressure by means of a manometer attached to a needle in the lumbar subarachnoid space relieved fever headache.

The fact that increasing the intracranial pressure decreased the intensity of the headache indicates that the mechanism of the headache in fever and that of the headache following injection of histamine are similar and that in both the intracranial arteries are the chief contributors to the pain. It is likely that the headache associated with acute infections, fever, sepsis and bacteremia has such an explanation.

It was possible to observe in experimental animals,[18] so prepared that the pial vessels could be visualized through a skull window, that the intravenous injection of foreign protein (typhoid vaccine) was followed by cerebral vasodilatation. Such vasodilatation was sometimes, but not always, associated with fever. Because of the use of barbiturates in inducing anesthesia, which was necessary to the experiment, fever was inconstantly obtained. No change in the pressure of the cerebrospinal fluid was observed, though sometimes the pressure became slightly higher. The vasodilatation was usually extreme, and it was suggested that headache would probably follow such a state.

COMMENT

To correlate the data on the various headaches under consideration, a comparison of the prototypes of each class of headache was made. Histamine headache was taken as the representative of a class which includes the headaches induced by amyl nitrite and foreign proteins and those associated with fever. The migraine headache was taken as representative of a class which includes, as well as the many varieties of migraine, the headache associated with hypertension.

These comparisons relate only to headache and waive consideration of other phenomena that may precede its onset. The histamine headache under discussion is that which results from intravenous injection of approximately 0.1 mg. of histamine phosphate.

The similarities between histamine headache and migraine headache are several. The quality and intensity of the pain in the two conditions are about the same; it is an aching pain, throbbing when intense. Many persons with migraine state that such headaches are less intense than those induced with histamine, but others who suffer severe attacks of migraine assert that the intensity is similar.

There are several factors which affect similarly the intensity of migraine and that of histamine headache. Thus, pressure on the common carotid artery decreases, and procedures that increase the systemic blood pressure increase, the intensity of both types of headaches. During the fall in blood pressure that immediately follows injection of histamine,

18. Wolff, H. G., and Fremont-Smith, F.: Unpublished data.

the intensity of a previously induced histamine headache is reduced. The migraine headache also is reduced in intensity during such a fall in blood pressure, to be accentuated when the blood pressure returns to its initial level. Both migraine and histamine headaches are often reduced in intensity by a tight head band.[19]

However, even though the similarities indicate that in the main the mechanisms of histamine and of migraine headache are related, the dissimilarities to be described are striking. First, the distribution and localization of the two types of headache are usually different. The histamine headache is always felt as a deep aching pain with minor superficial components. The migraine headache, though a deep ache, commonly feels more superficial.

Second, the histamine headache is always bilateral, usually generalized and commonly worse in the frontal and the temporal region, although it may be severe, or may even start, in the back of the head. In contrast, the migraine headache is characteristically unilateral, at least in onset, though later it may become bilateral. The site of the migraine headache varies. Though temporal and frontal headaches are more common, many subjects always experience the major part of the pain in the occipital or the suboccipital region. The headache during any given attack is usually highly circumscribed.

Third, the histamine headache is little influenced by ligation of the middle meningeal artery or by compression of the temporal, frontal, postauricular or occipital artery.[19] On the other hand, the migraine headache, if in the temporal or the parietal region, is often reduced in intensity, and sometimes actually eliminated, by obliteration or ligation of the temporal or the middle meningeal artery.

Fourth, the histamine headache is not prevented, decreased in intensity or shortened by ergotamine given sufficiently soon for it to have full effect at the time of the injection of histamine.[20] In this regard, the migraine attack contrasts sharply with the histamine headache, for in adequate amount ergotamine tartrate, given intravenously or intramuscularly, prevents, significantly reduces or terminates migraine headache. These facts may be related to the observation that in the head histamine dramatically affects the cerebral arteries,[21] whereas ergotamine tartrate affects principally the branches of the external carotid arteries.[22]

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19. Schumacher, G. A.; Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Further Analysis of Histamine Headache and Its Pain Pathways, Arch. Neurol. & Psychiat. **44**:701 (Oct.) 1940.

20. Graham and Wolff.[1b] Lennox, von Storch and Solomon.[4]

21. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929.

22. Pool, J. L., and Nason, G. I.: Cerebral Circulation: XXXV. The Comparative Effect of Ergotamine Tartrate on the Arteries in the Pia, Dura and Skin of Cats, Arch. Neurol. & Psychiat. **33**:276 (Feb.) 1935.

The fifth dissimilarity between the two types of headache is seen in the effect of increasing the venous pressure by compression of the jugular vein. This procedure promptly diminishes the intensity of the histamine headache,[7a] but has a variable and indefinite influence on the intensity of the migraine headache. The probable explanation is that the increased venous pressure, by increasing the cerebrospinal fluid pressure, increases extramural support to the relaxed pial arteries and curtails distention and pain. The fact that relief in migraine headache does not occur indicates again that the pial and cerebral arteries are less involved in the migraine headache than in the histamine headache.

The sixth difference is a corollary of the fifth and concerns the effect of increasing the cerebrospinal fluid pressure directly. The intensity of the histamine attack is promptly reduced by this procedure,[7] but the intensity of the migraine headache is not.[10]

The seventh point of difference is the appearance of the subjects during migraine headache as compared with that of persons having histamine headache. Commonly, in association with migraine headache in the temporal or the parietal region the temporal artery is distended on the affected side. No such difference between the two sides is observed in subjects with histamine headache.

Eighth, during the histamine headache the amplitude of pulsations both of arteries of the scalp and of the intracranial arteries is greatly increased, and the amplitudes of both groups of arteries decrease as the headache recedes. In contrast, during the migraine headache the amplitude of pulsations of only the scalp arteries is increased, and it decreases as the headache becomes less intense. It is striking that the amplitude of intracranial pulsations does not change as the migraine headache recedes.

CONCLUSIONS

From these considerations the following inferences seem justified. For the histamine headache, it is likely that the cerebral branches of the internal carotid, basilar and vertebral arteries at the base of the brain are primarily responsible. To the migraine headache, however, the extracranial, and possibly the dural, branches of the external carotid artery are the chief contributors.

TREATMENT OF UNILATERAL PARALYSIS AGITANS BY SECTION OF THE LATERAL PYRAMIDAL TRACT

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The syndrome of alternating tremor of rest has been recognized as an incapacitating disease since the day of Celsus. Parkinson,[1] whose brilliant essay established its clinical characteristics, pointed out that, in many instances at least, brief periods of complete relief occur spontaneously, for example, after change of posture, under the stress of excitement or in carrying out complicated learned motor patterns. It would appear reasonable, therefore, to hope that some form of treatment might be devised which would mitigate the symptoms without seriously impairing normal function. This possibility has appeared even more attainable since the epidemic of encephalitis, which has been followed by an increase in the incidence of cases of alternating tremor in relatively young patients, in many of which, however, no history of encephalitis can be elicited. The outlook for satisfactory restitution would appear to be better in such cases than in those of the senile group reported by Parkinson.

So far, the accepted treatment for paralysis agitans has been pharmacologic. Drugs of the atropine series (Charcot, 1867, cited by Ordenstein[2]) sometimes produce spectacular improvement. To be effective, they often have to be given in doses much larger than are suggested in the pharmacopeia. Particular attention has recently been paid to wine of Bulgarian belladonna,[3] but in this clinic at least it appears to be effective in few cases in which benefit is not derived from the older drugs. The synthetic drugs of the same series and harmine, bulbocapnine and cobra venom, all of which have been recom-

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1. Parkinson, J.: An Essay on the Shaking Palsy, London, Sherwood, Neely & Jones, 1817; in Ostheimer, A. J.: An Essay on the Shaking Palsy, by James Parkinson, M.D., Member of the Royal College of Surgeons, with a Bibliographic Note Thereon, Arch. Neurol. & Psychiat. **7**:681-710 (June) 1922; M. Classics **2**: 964-998, 1938.

2. Ordenstein, L.: Sur la paralysie agitante et la sclérose en plaques généralisée, Thesis, Paris, no. 254, 1868, p. 31.

3. Gayle, R. F.: The Treatment of Parkinsonism with a Preparation of Belladonna Root, Virginia M. Monthly **66**:701-710, 1939.

mended, have failed in this vicinity to substantiate the claims made for them. Pilocarpine nitrate, in doses of ⅛ grain (0.008 Gm.) three times daily by mouth, sometimes mitigates the toxic effects of the drugs of the atropine series, and so permits the use of larger doses. Benzedrine sulfate (amphetamine) in doses up to 20 mg. daily is a useful adjuvant, especially effective against narcolepsy, oculogyric crises and certain other tics which are common complications of paralysis agitans.[4] The intravenous injection of curare (West and others[5]) produces temporary amelioration of symptoms.

PREVIOUS ATTEMPTS AT SURGICAL TREATMENT, WITH REVIEW OF LITERATURE

Older Surgical Procedures.—All of the measures mentioned are often without durable result. In cases of severe localized tremor surgical intervention has appeared justified. There are indeed few diseases which drive their victims more insistently toward any prospect of relief.

Since Walshe[6] had shown that injection of procaine into sensory nerves mitigates rigidity, Pollock and Davis[7] cut the posterior roots in a case of rigidity and tremor of one arm. The rigidity was diminished, but not the tremor, which was altered in amplitude and rate. The arm assumed a position of contracture. Foerster and Gagel[8] obtained a similar result in a similar case by the same procedure. They also cut the anterolateral column without producing any definite change in the symptoms. Puusepp[9] also reported cases in which rigidity but not tremor was ameliorated by partial deafferentation.

On the hypothesis that the tremor and accompanying rigidity are of reflex origin, Puusepp,[10] in 1930, cut the column of Burdach in a

4. Solomon, P.; Mitchell, R. S., and Prinzmetal, M.: Use of Benzedrine Sulfate in Postencephalitic Parkinson's Disease, J. A. M. A. **108**:1765-1770 (May 22) 1937.

5. Kairiukschtis, V., and Kutorga, V.: Versuche die Muskelrigidität beim Parkinsonismus durch Injektion von Kurare zu beseitigen, München. med Wchnschr. **74**:537-538, 1927. West, R.: Pharmacology and Therapeutics of Curare and Its Constituents, Proc. Roy. Soc. Med. **28**:565-578, 1935.

6. Walshe, F. M. R.: Observations on the Nature of the Muscular Rigidity of Paralysis Agitans and on Its Relationship to Tremor, Brain **47**:159-177, 1924.

7. Pollock, L. J., and Davis, L.: Muscle Tone in Parkinsonian States, Arch. Neurol. & Psychiat. **23**:303-319 (Feb.) 1930.

8. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

9. Puusepp, L.: Chirurgische Neuropathologie, Dorpat, Krüger, 1932, vol. 1, pp. 416-417.

10. Puusepp, L.: Cordotomia Posterior Lateralis (Fasc. Burdachi) on Account of Trembling and Hypertonia of the Muscles in the Hand. (To the Physiology of the Posterior Columns in a Human Body), Folia neuropath. Estoniana **10**:62-66, 1930.

case of paralysis agitans involving one arm. The rigidity was decreased, but not the tremor; there was loss of sense of touch as well as that of movement in the arm. The same result followed two similar operations in the hands of Rizzatti and Moreno.[11]

Section of the anterior column, effective against athetosis, did not affect alternating tremor in the 5 cases in which it has been tried in this clinic.[12] Mashanskiy,[13] however, reported improvement (in most instances slight or temporary) in 6 of 18 cases in which he performed a similar operation. The technic which he employed in most of the cases involved section in the prepyramidal region, which may conceivably have injured the pyramidal tract also. As will be seen later, even partial destruction of the pyramidal tract sometimes greatly modifies alternating tremor.

Paralysis agitans is sometimes profoundly modified by total thyroidectomy (Myerson and Berlin,[14] Silbermann and Singer [15] and Cutler [16]). The drawbacks are obvious, and the method has not found wide acceptance.

The operation of sympathetic ramisectomy for rigidity was founded on erroneous premises and has been abandoned in most neurologic clinics.

Operations on the Cerebral Cortex.[17]—In a case of Parkinson's the tremor disappeared after hemiplegia. The same phenomenon has been observed many times since. Aring and Fulton [18] were able to produce

11. Rizzatti, E., and Moreno, G.: Cordotomia laterale posteriore nella cura della ipertonie extrapiramidali postencefalitische, Schizofrenie **5**:117-122, 1936.

12. Putnam, T. J.: Results of Treatment of Athetosis by Section of Extrapyramidal Tracts in the Spinal Cord, Arch. Neurol. & Psychiat. **39**:258-275 (Feb.) 1938.

13. Mashanskiy, F. I.: Traitement chirurgical des mouvements involontaires des extrémités appliqué au parkinsonisme post-encéphalitique, J. de chir. **46**:877-899, 1935.

14. Myerson, A., and Berlin, D. D.: Case of Postencephalitic Parkinson's Disease Treated by Total Thyroidectomy, New England J. Med. **210**:1205-1206, 1934.

15. Silbermann, M., and Singer, R.: Ueber die totale Thyreoidektomie bei Gefässerkrankungen, Cong. internat. de l'Union thérap. **1**:383-390, 1937.

16. Cutler, E.: Personal communication to the author.

17. Mashanskiy [13] stated: "[This] clinic . . . has tried many times, and over a series of years, to solve the problem . . . of the operative treatment of . . . extrapyramidal hyperkinesis. Horsley's operation, alcoholization of cortical centers and the [subcortical] pyramidotomy of Polienov have been tried. . . . But the struggle . . . against parkinsonian tremor has remained an unresolved problem." I have been unable to obtain Polienov's articles or reprints.

18. Aring, C. D., and Fulton, J. F.: Relation of the Cerebrum to the Cerebellum: II. Cerebellar Tremor in the Monkey and Its Absence After Removal of the Principal Excitable Areas of Cerebral Cortex (Areas 4 and 6a, Upper Part); III. Accentuation of Cerebellar Tremor Following Lesions of Premotor Area (Area 6a, Upper Part), Arch. Neurol. & Psychiat. **35**:439-466 (March) 1936.

a long-lasting, but not permanent, tremor of rest in monkeys by section of the superior cerebellar peduncle, and found that it could be increased by resection of the motor cortex proper, or even more by removal of both the motor and the premotor cortex.

Reasoning from these facts, Bucy and Case [19] performed ablation of the motor and premotor cortex in a case of severe alternating tremor of one arm of traumatic origin. The tremor has been completely relieved for two years, and the cortical monoplegia which is left is far less annoying to the patient than his preoperative state. Klemme [20] has achieved striking results in a large series of cases by removal of frontal cortex anterior to the electrically excitable region. Details are not yet available. There is an obvious discrepancy between Klemme's results and those obtained experimentally by Aring and Fulton. Using a method similar to that of Klemme, White [21] obtained only partial relief in a similar case. In a case of unilateral paralysis agitans reported by Sussmann,[22] the corresponding motor cortex was exposed, and it was found that pressure on the electrically excitable area stopped the tremor. The region so delimited was resected. There was complete, but only temporary, cessation of tremor.

Meyers [23] has described cases in which relief of tremor was secured by resection of a portion of the caudate nucleus. Since cortical incisions were made to reach the ventricle, the result is somewhat difficult to evaluate.

Since so few cases of cortical resection for tremor are on record and there is some question as to which area should be removed, the following cases are reported. The operative technic employed in the first case might be of use in other operations on the cortex aimed at control of involuntary movements.

REPORT OF TWO CASES IN WHICH RESECTION OF AREA 6 GAVE RELIEF

CASE 1.—George S., aged 29, a policeman, was referred by Dr. Stanley Cobb. In November 1929 he was thrown from a motorcycle, striking his head. About three weeks later his left hand and arm began to tremble. The tremor became constant and continued with little change up to the time of his admission for operation to the Neurological Unit of the Boston City Hospital. He was compelled by the tremor to give up active duty outdoors, and became a police photographer.

On examination, he was found to be a healthy man, of better than ordinary physique. The sole abnormality was an alternating tremor of rest (fig. 1) in the

19. Bucy, P. C., and Case, T. J.: Tremor: Physiologic Mechanism and Abolition by Surgical Means, Arch. Neurol. & Psychiat. **41**:721-746 (April) 1939.

20. Klemme, R.: Personal communication to the author.

21. White, J. C.: Personal communication to the author.

22. Sussmann, E.: Personal communication to the author.

23. Meyers, R.: A Surgical Procedure for Postencephalic Tremors, Arch. Neurol. & Psychiat., to be published.

left forearm and hand, which was diminished by voluntary movement (fig. 2 *B*). There was no weakness, rigidity or abnormality in the reflexes. Rapid opening and closing of the affected hand could, however, be carried out only a few times before stiffness set in. There was slight immobility of the left side of the face.

Electromyograms (fig. 2 *A*) showed that the tremor was regular, at a rate of 4.5 per second, and was produced by staccato bursts of activity alternately in protagonists and antagonists, with complete relaxation between.

When the possibility of operative relief was explained to him, the patient eagerly accepted the risks involved. No economic gain was in prospect, as his position was assured in any case, but he stated he found the tremor so annoying that he was willing to go to great lengths to be free of it. As the leg was not

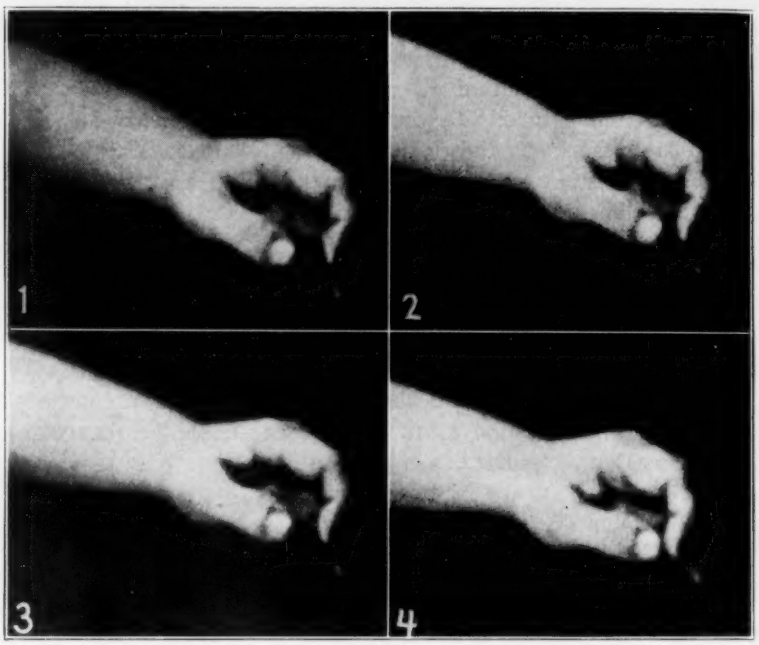

Fig. 1 (case 1).—A cycle of alternating movements of the fingers (frames from a moving picture seven sixty-fourths of a second apart). Note how closely the end positions are reproduced.

involved and the affected arm was the left one, a cortical operation appeared preferable to chordotomy of the type to be described later.

Operation.—This was performed on May 20, 1939, with the use of anesthesia maintained with morphine and scopolamine and local anesthesia. A high-placed bone flap was turned down over the right frontoparietal region, adjacent to the longitudinal sinus. The patient was given a small dose of sodium evipal (a sodium salt of n-methyl-C-C-cyclohexamylmethyl barbituric acid) intravenously while the base of the flap was being broken and the meningeal artery secured. When the dura was reflected an atrophic area of the cortex, covered by gray, cobweb-like arachnoid, was observed in the first frontal convolution near the sinus (fig. 3 *A*).

The motor cortex was mapped out by means of a current from an induction coil just strong enough to produce contraction of the temporal muscle. The area corresponding to the arm was found at the vertex; the "leg" region could not be reached. Stimulation of the region of the atrophic area produced mild generalized seizures with unconsciousness.

When the cortex had been thoroughly explored, about 2 cc. of a 1 per cent solution of procaine hydrochloride was injected by means of a fine needle into the postcentral ("sensory") area for the arm. No objective or subjective change resulted. Next, the "premotor" region about the scar was similarly infiltrated,

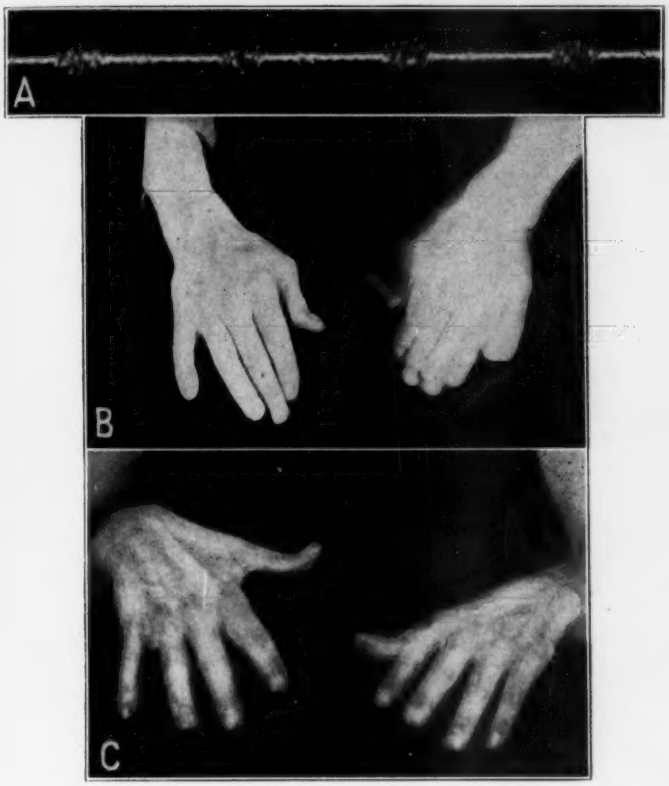

Fig. 2 (case 1).—*A*, electromyogram from the biceps muscle; time in one-sixtieth second intervals. *B*, hands before operation; exposure, one-fifth second. *C*, hands after operation; exposure, one-fifth second.

without result; if anything the tremor became more violent. Firm pressure was exerted with a spatula on the precentral convolution. After a delay of about three seconds the patient stated that his arm felt weak, and simultaneously the tremor stopped. This maneuver was repeated five times, always with the same result. Finally, 2 cc. of the solution of procaine hydrochloride was injected into the region (almost certainly not to the depth of the sulcus), and the tremor remained arrested. After a delay of ten minutes a strip of the infiltrated cortex

was resected by means of the cutting current. Its location is shown in figure 3 *B*. It measured approximately 1 cm. in anteroposterior width, 0.8 cm. in depth, including therefore a few millimeters of white matter, and 2.5 cm. in length.

Course.—The postoperative course was smooth. There was a typical flaccid monoplegia of the arm without sensory changes, which gradually improved over the next month. At the time of writing, four months after operation, there is little weakness but marked awkwardness of the hand and arm; the member,

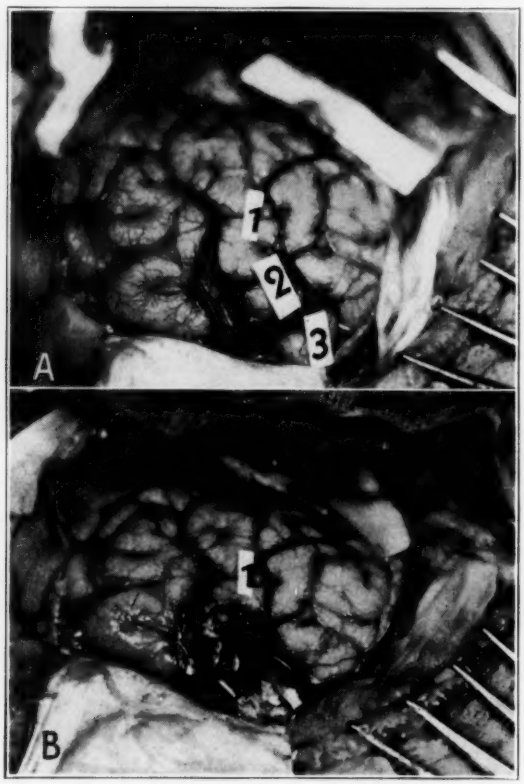

Fig. 3 (case 1).—Cortex exposed (*A*) before excision. *1* indicates the "face," *2* the "hand" and *3* the "shoulder" representation. Note that *3* lies adjacent to the sinus. *B*, cortex after excision.

however, is useful. On the whole, there is more disability than results from section of the lateral pyramidal tract. There has been only a suggestion of tremor (fig. 2 *C*). If it returns to any greater degree the patient is prepared for a reexploration and further extirpation.

Pathologic Condition.—Dr. Leo Alexander reported on the specimen (fig. 5) removed. Gross Description: The specimen consisted of a block of tissue, measuring 12 by 20 mm., which was fixed in alcohol and solution of formaldehyde. The tissue was brownish and incrustated with fluid blood.

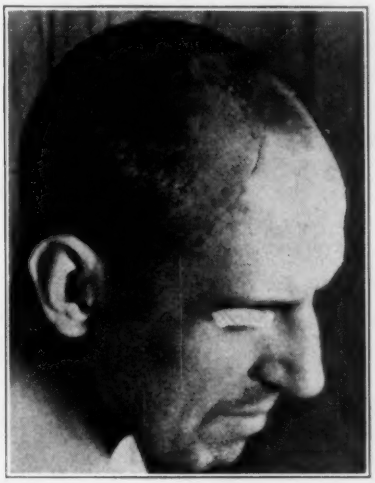

Fig. 4 (case 1).—Scar of incision at time of discharge.

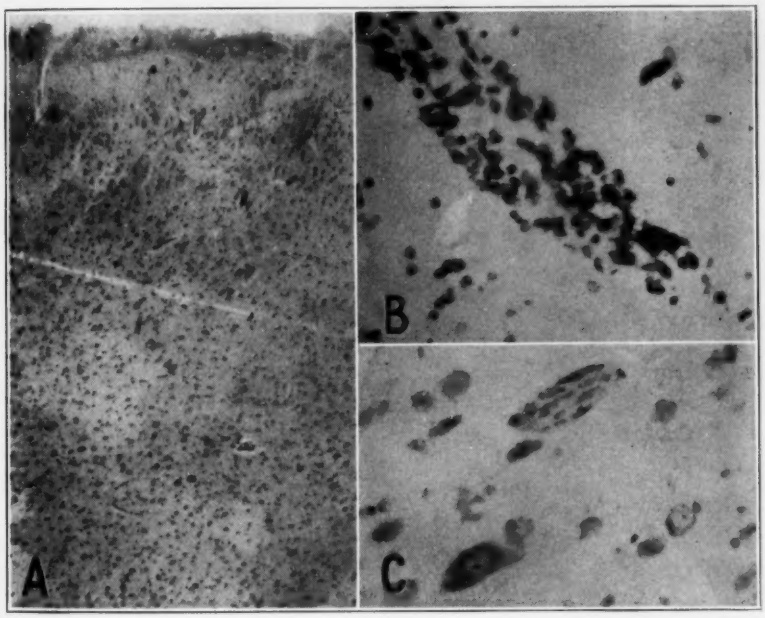

Fig. 5 (case 1).—Histologic specimen. *A*, low power view; *B*, vessel infiltrated with phagocytic cells, and *C*, one of the few Betz cells encountered.

Microscopic Description: The sections taken through this block showed cerebral cortex of agranular type. The appearance of the sections throughout the anterior part of the block was consistent with that of area 6. Most of the posterior part of the block also passed through area 6, but at one margin the presence of a small number of giant pyramidal cells, of which altogether three were seen in two sections, indicated that this part of the block included the anterior edge of area 4. The three giant pyramidal cells seen measured 24 by 40, 20 by 48 and 20 by 48 microns in diameter, respectively.

Many of the larger cells in area 6 showed a slight degree of swelling, which was possibly incidental to the trauma of removal.

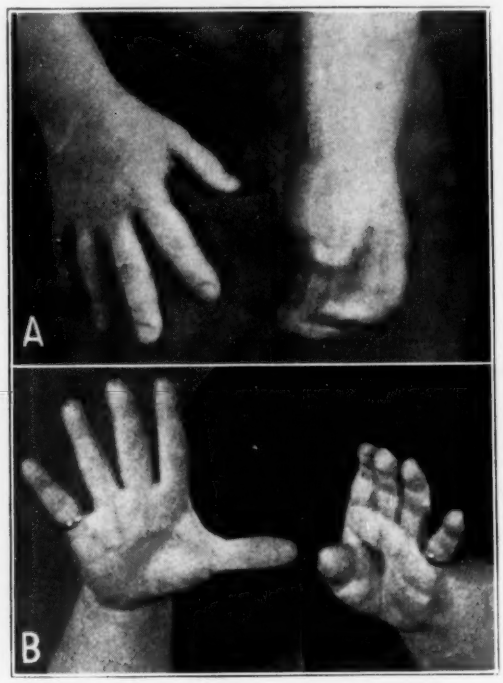

Fig. 6 (case 2).—Patient's hands (*A*) before and (*B*) after operation. Exposure, one-fifth second.

Summary: The sections involved cortex from area 6 and from a small adjacent portion of area 4.

In a second case the same procedure was planned, but could not be as satisfactorily carried out, because the tremor ceased while the patient was under the anesthesia.

Case 2.—Marian McM., aged 45, who was referred by Dr. B. H. Ragle, in 1925 suffered an acute febrile illness with vomiting, which lasted a few days. As she recovered she found that her left hand was weak. A year and a half later it began to tremble, so severely that she had to give up her work as secretary and become a telephone solicitor. Two years later a very mild tremor

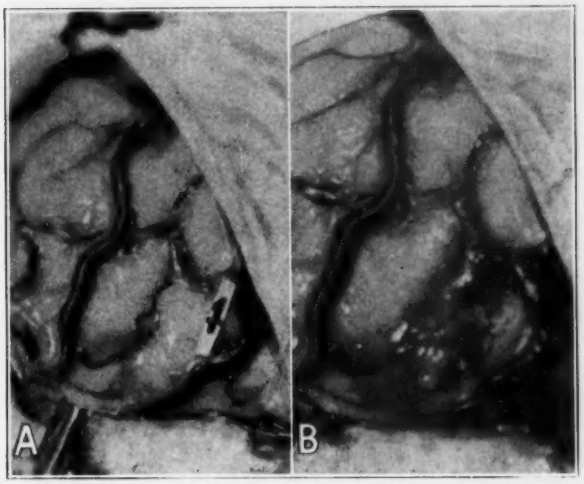

Fig. 7 (case 2).—Cortex (*A*) before and (*B*) after excision of tissue. *1* marks the "hand" region. Notice it is adjacent to the sinus (edge of exposed area).

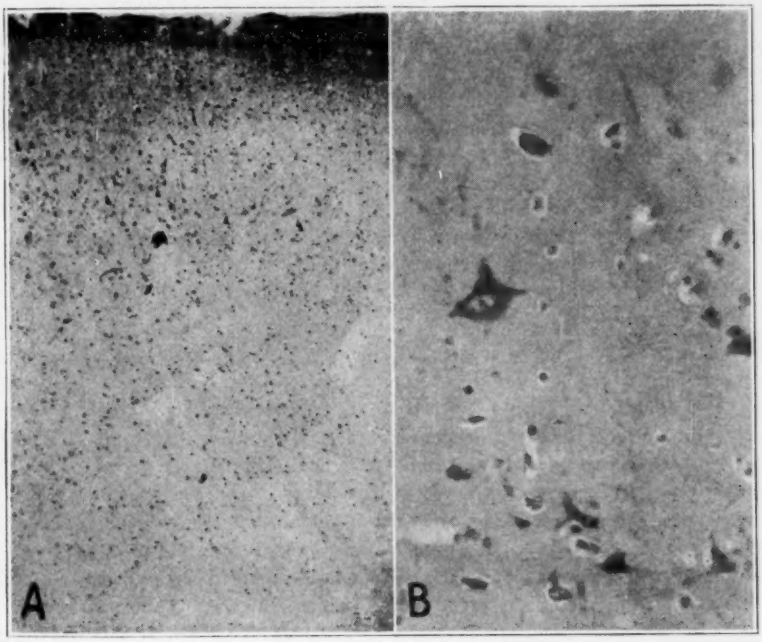

Fig. 8 (case 2).—Sections from the specimen excised. High power view (*B*) shows one of the few Betz cells seen.

affected the left leg also, but caused her little inconvenience. The tremor of the arm, however, became the dominant fact in her life. She became extremely sensitive about it and would seldom go out of the house, although previously she had been gay and normally social. Even when alone she was driven to desperation by the constant incontrollable movement, and spent most of her time restraining the left hand with the right. She had broken an engagement on account of her disability. Treatment with large doses of scopolamine, benzedrine and dilantin sodium had no effect on the tremor.

She was an intelligent, alert, cooperative woman, who appeared young for her age. The left arm was the seat of a continual tremor, during attempts at relaxation as well as volitional activity. The tremor was of the characteristic alternating type and was uniform in rate (fig. 6*A*). The hand was most active, next the arm and shoulder. Tremor of the left leg was slight, and disappeared in walking. There was slight weakness of the left side of the face. Rapid winking quickly became impossible, and alternate opening and closing of the hand produced a characteristic "freezing." The grip was powerful. Results of neurologic and general physical examination were otherwise not remarkable.

The patient eagerly accepted the risks of operation when the situation was explained to her.

Operation.—This was performed on Aug. 5, 1939, almost precisely as in the previous case. Unfortunately, however, the tremor was arrested by the preliminary medication, and no maneuvers would bring it back. When the cortex was exposed there was observed in this case also mild atrophy of the anterior portions of the frontal convolutions, though it was less marked than in case 1. The "arm" area was located by liminal electrical stimulation from an induction coil with a bipolar electrode. It lay at the vertex, adjacent to the longitudinal sinus. Application of the current for over a second in any one spot caused a mild convulsion.

As there was no means of deciding which area was responsible for the tremor, a strip was removed from the electrically stimulable precentral cortex, near the edge of the central sulcus (fig. 7). Particular care was exercised, by the use of Horsley's method of subpial resection, to avoid injury to the blood supply. The specimen measured 2 cm. in (vertical) length, by 0.4 cm. in width by 0.6 cm. in depth. It barely included the white matter (fig. 8). When the wound was dry the dura was sewn in place and the bone flap replaced.

Course.—The patient had a mild convulsion on the day after operation, but her recovery was otherwise uneventful. She had flaccid monoplegia, with slight weakness of the left side of the face and the left leg, but no sensory changes. Voluntary movement began to return to the left arm four days after operation, and at the end of three weeks she was able to make a feeble fist. A slight intention tremor appeared at this time (fig. 6*B*). At the last examination, six weeks after the operation, the tremor was no worse, and the patient was able to raise her hand above her head and to use it for many purposes. The patient was last seen in March 1940. The remnant of the tremor persisted as at the previous examination. The usefulness of the hand had decreased rather than increased, and definite "lead pipe" rigidity had appeared in the fingers, wrist and elbow.

Histologic Observations.—The cortex removed appeared thinner and less cellular than normal (fig. 8*A*). There were no signs of infiltration or fresh degeneration. Betz cells were rare and were found scattered in the deeper layers (fig. 8*B*).

The specimen of cortex was therefore presumably almost entirely from area 6 of Brodman. Only a small fraction of area 4 can have been damaged by the extirpation.

REPORT OF SIX CASES OF UNILATERAL TREMOR TREATED BY SECTION OF LATERAL PYRAMIDAL TRACT IN CERVICAL PORTION OF CORD: RATIONALE OF TREATMENT

The syndrome of athetosis is sharply differentiated from that of alternating tremor by the electromyographic pattern, although the two may coexist. In athetosis there is a normal polyrhythmic blend of motor unit discharges, but opposed groups of muscles contract simultaneously.[24] In alternating tremor the movement is produced by discrete bursts of synchronous discharges, evenly spaced, with an interval of relaxation, alternately in flexors and extensors.[25] It has already been pointed out that extensive destruction of long descending nonpyramidal tracts in the spinal cord greatly decreases movements of an athetoid character, but has no influence on alternating tremor. It seemed reasonable to believe, therefore, that impulses passing along the pyramidal tract were essential to the production of alternating tremor.[12] Further support for this conception was given by the experiments of Aring and Fulton [18] previously cited, and finally by the case of Bucy and Case.[19] Sections of the lateral pyramidal tract in monkeys by Rothmann [26] produced little disability, so that there seemed reason for believing that it might be well tolerated in human beings.

For some years a search has been made for a case in which a unilateral tremor was sufficiently incapacitating to justify the possible risks involved in cutting the pyramidal tract. The following case appeared to meet the requirements.

CASE 3.—Lillian C., aged 32, unmarried, was first admitted to the wards of the neurologic unit on Feb. 24, 1938. She had considered herself well until sixteen years previously, when she awoke one morning with a tremor of the right arm and right leg. This had always prevented her from seeking employment, and indeed from leaving the house, except rarely. It had gradually increased in severity, in spite of treatment with various medicines, including large doses of stramonium.

On examination, it was obvious that the patient was somewhat retarded mentally. General physical examination and routine laboratory tests gave normal results.

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24. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Athetosis and Sydenham's Chorea, Arch. Neurol. & Psychiat. **44**:517-532 (Sept.) 1940.

25. Hoefer, P. F. A., and Putnam, T. J.: Action Potentials of Muscles in Rigidity and Tremor, Arch. Neurol. & Psychiat. **43**:704-725 (April) 1940.

26. Rothmann, M.: Ueber die Ergebnisse der experimentellen Ausschaltungen der motorischen Funktion und ihrer Bedeutung für die Pathologie, Ztschr. f. klin. Med. **48**:10-29, 1903.

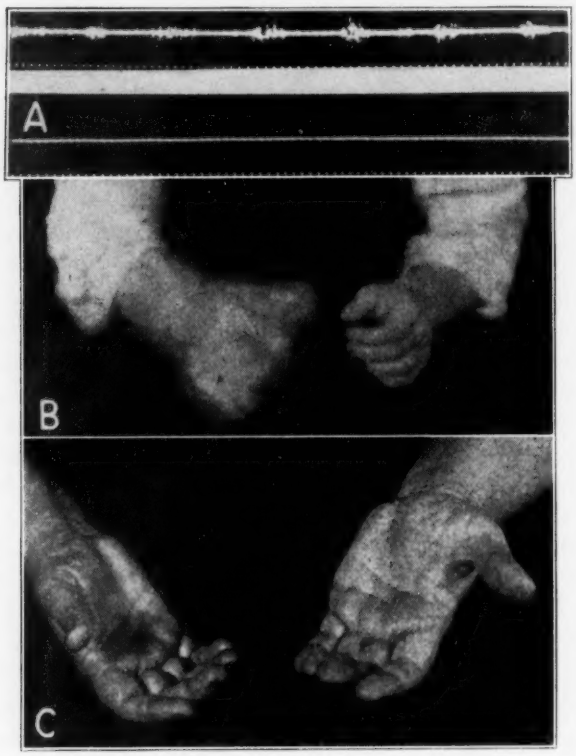

Fig. 9 (case 3).—*A*, electromyograms (above) before and (below) after operation. Time in one-sixtieth second intervals. Hands (*B*) before and (*C*) after operation (background retouched).

Fig. 10 (case 3).—Habitual gait before operation. From a moving picture film, frames one-sixteenth second apart (background retouched).

Interest centered chiefly about the condition of the right arm and leg. The arm was in a constant coarse tremor, with an excursion of about 3 cm. at the tips of the fingers (fig. 9 *B*). It was held slightly flexed and somewhat rigid (fig. 9 *B*). The tremor was somewhat increased by an attempt to hold the arm still or to carry out intentional acts. The patient could not use the right hand in writing, eating, drinking from a glass of water or buttoning a button. She generally used the left hand, which had become the dominant one.

The right leg also showed a constant, though milder, tremor when she sat still. In walking she was seen to have a curious high-stepping, ticlike gait. The right foot was raised rather rapidly to the level of the left knee with a rotary motion and then set on the floor inverted with the toe first (fig. 10). Walking, therefore was excessively tedious and difficult for her. There was no propulsion.

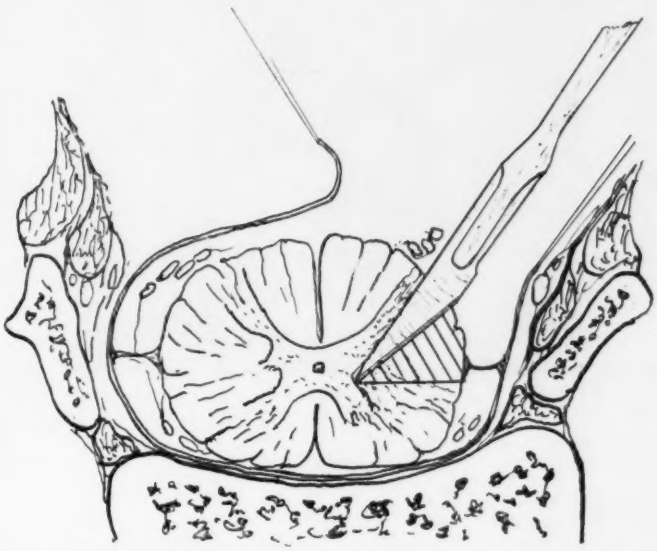

Fig. 11.—Diagram illustrating section of the lateral pyramidal tract.

The deep reflexes were slightly increased in the right arm and leg, and there was a questionable Babinski sign but no clonus. There was a suggestion of cog-wheel rigidity on passive movement of the elbow or knee.

Electromyograms showed characteristic discrete bursts of impulses, at the rate of 5.8 per second (fig. 9, upper tracing of *A*).

When the conceivable possibility of operative relief was explained to her, she eagerly grasped the opportunity.

Operation.—This was carried out on March 4, 1938, under anesthesia induced by avertin with amylene hydrate. A midline incision was made over the spines of the cervical vertebrae, which were cleaned with the cutting current. The laminas of the third and fourth cervical vertebrae were removed. The dura was opened well to the right of the midline. The small sharp-pointed Bard-Parker knife (no. 11) was inserted into the lateral column of the fourth cervical segment adjacent to the point of exit of the posterior root, at an angle of about 15 degrees from the vertical, with its edge outward. It was pushed in to a depth of 4 mm.,

and the resulting incision measured about 3 mm. on the surface. There was practically no bleeding, and the operation was completed without incident.

Course.—On the following day it was found that the left arm and leg were flaccid, and only the slightest movements of the fingers were possible. There was

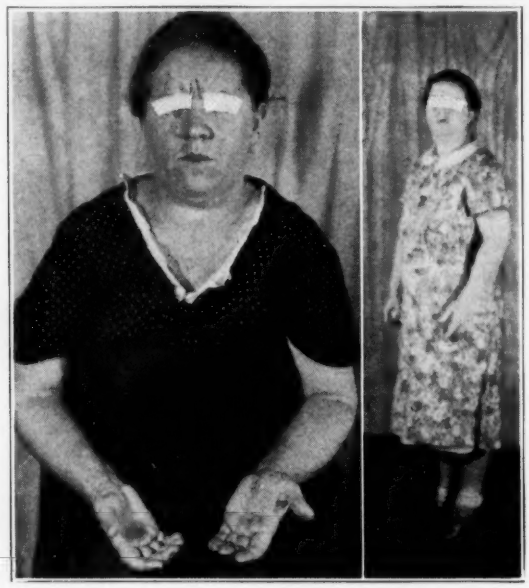

Fig. 12 (case 3).—Patient after the last operation. Note the normal posture.

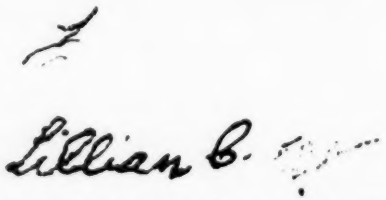

Fig. 13 (case 3).—Patient's signature after the last operation. She was unable to write before operation.

a striking diffuse hyperpathia of the radial side of the right hand, which gradually disappeared in the course of a week. Strength rapidly returned, so that on the eighteenth day the patient was able to walk and to use her hand for drinking and writing.

Six weeks after operation the situation was reviewed. The strength of the arm and hand had returned to approximately half its preoperative level. Individual movements of the fingers were possible; the patient could use the hand for writing and for drinking from a tumbler. Walking was greatly improved, the gait being now of a typical mild hemiparetic type.

Neurologic examination showed that all deep reflexes on the right side were elicited, with a greatly lowered threshold; they were quick and powerful and had

a tendency to spread beyond their normal zone. The Hoffmann, Babinski, Oppenheim, Mendel-Bechterew and Rossolimo phenomena and ankle clonus were elicited. The right abdominal reflex was absent. There were no sensory changes. No tremor was observable at rest. Electromyographic tracings showed a barely perceptible rhythmic discharge (fig. 9, lower tracing in *A*). A trifling unsteadiness occurred with intentional effort. There was no rigidity.

This happy state of affairs was not permanent, however. The tremor gradually returned to the hand, reaching a stationary level of about one-half its original intensity, four months after operation. The improvement of the leg was retained.

Second Operation.—Eight months after the first operation, on Oct. 10, 1938, a more radical operation was undertaken in the hope of controlling the residual tremor. The wound was reopened and a knife similar to that used in the first operation was inserted in the same segment in a similar direction. This time, however, the point of the knife was swept out laterally to the horizontal meridian of the cord, thus transecting a triangular area just lateral to the posterior horn, measuring approximately 4 mm. along each side (fig. 11). The depth of the incision (4 mm.) was demonstrated to witnesses by inserting in it the tip of an ordinary scalpel.

Course.—The patient again made an uneventful recovery. The strength of the arm and leg returned more slowly and less completely than before, passing through the same stage of flaccidity.

The late result, a year after the second operation, is as follows: The patient has about one-third the preoperative strength of the right hand and arm. She can move the fingers individually, and write (figs. 12 [left] and 13). She can use the hand for eating, dressing herself and other purposes, though more awkwardly than the left and with perceptible tremor. The gait is definitely hemiparetic, but she can walk several blocks and is constantly improving. Ability to walk is certainly far better than before the first operation.

There is no rigidity on passive motion, but slight spasticity of "antigravity" muscles is apparent. The deep reflexes are definitely exaggerated and spread beyond the normal zone. There is wrist, patellar and ankle clonus. The abnormal reflexes already mentioned are still present. There is no tremor of rest (figs. 9 *C* and 12, left) but a little unsteadiness is brought out by volitional movement. The patient feels that her life has been transformed.

Partial section of the lateral pyramidal tract, substantially as in the first operation in case 3, has been carried out in 3 other cases.

CASE 4.—James R., a carpenter aged 55, was admitted to the Boston City Hospital on April 4, 1938. He had considered himself well until 1933, when he began to have tremor, stiffness and weakness of the left hand, which gradually progressed until it prevented him from working.

Examination showed him to be well nourished and sturdy and in good condition except for a blood pressure of 150 systolic and 90 diastolic and the tremor of the left hand. The tremor was a typical alternating one, with a rate of 7.1 per second (fig. 14 *A* and *B*) and a wide range, which was increased by voluntary effort.

He could not use his left hand in buttoning his clothes or in drinking from a glass. Most trying, however, was the constant annoyance of the involuntary movement, which "got on his nerves."

There was slight palpable rigidity of the elbow. Alternating movements could be carried out only briefly with the hand. There were a barely perceptible tremor of the right hand and of both legs and slight immobility of the face.

As no relief was obtained from drugs of the scopolamine group (including two synthetic compounds, genoscopolamine and syntropan) or from injections of cobra venom, the patient gladly accepted operation.

Operation.—This was performed on April 7, 1938. An incision, 4 mm. deep and 2 mm. on the surface, lateral to the posterior horn was made at the third cervical level.

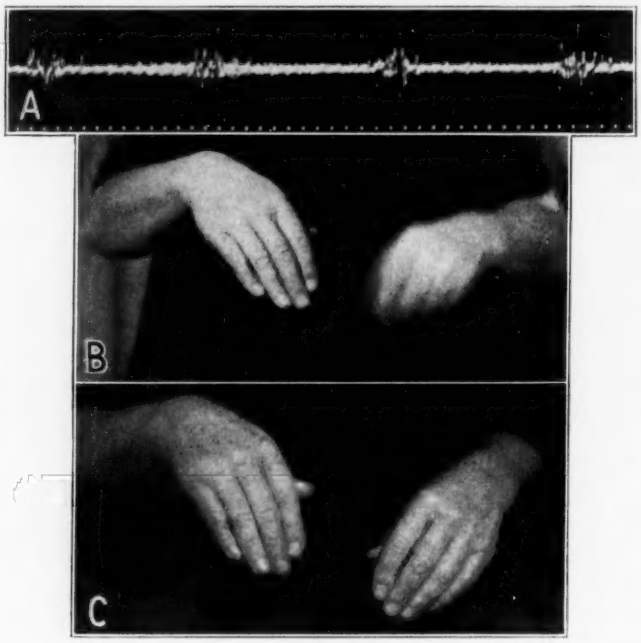

Fig. 14 (case 4).—*A*, electromyogram before operation. Time in one second intervals. Below, patient's hands (*B*) before and (*C*) after operation. Exposure, one-fifth second.

Course.—The patient made a good recovery, and could move his fingers individually the day after operation. A zone of analgesia was demonstrable over the thumb and forefinger of the right hand; this gradually disappeared.

The strength and control slowly returned to the left arm and leg, and with it the signs of spasticity, exactly as outlined in case 3, and a slight tremor (fig. 14 *C*). When the patient was last seen, twelve months after operation, usefulness of the left hand was distinctly improved as compared with its preoperative state. The gait, on the other hand, was slightly less good, because of the hemiparesis. The tremor of the right hand was becoming more noticeable. The patient had been able to work, however, for a brief period, when opportunity offered, for the first time in two years.

CASE 5.—Theresa S., a schoolgirl aged 16, was seen at the Massachusetts General Hospital on Aug. 10, 1938, by permission of Dr. R. S. Schwab and Dr. J. C. White. Three years previously she had awakened one morning to find that she had a tremor of the left arm and leg. This grew progressively somewhat more severe, up to the time of her admission to the hospital. Her chief complaint was that the tremor "got on her nerves."

Examination showed a healthy, but somewhat retarded, girl, with a typical alternating tremor of the left arm and leg (fig. 15 *A*). The right side was also slightly involved. The tremor was somewhat diminished by volitional movement.

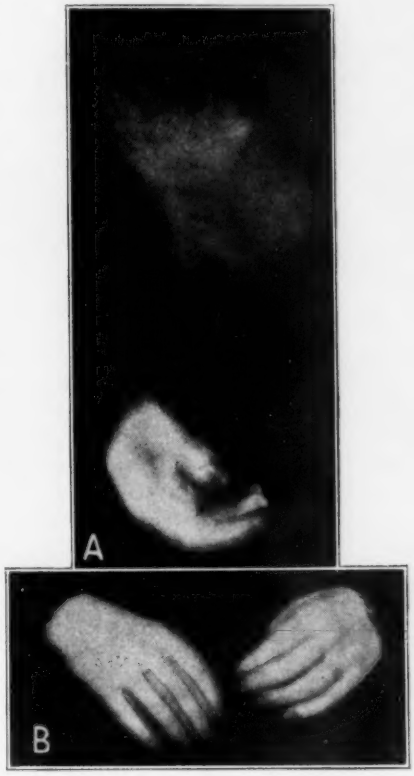

Fig. 15 (case 5).—Patient's hands, (*A*) before and (*B*) after operation. The upper blur in the preoperative photograph is the left hand. Exposure, one-fifth second; background retouched.

The Babinski reflex was positive on the left, and there was slight rigidity of the left arm and leg. Neurologic examination otherwise revealed nothing remarkable.

The prospects of operation were explained to the patient, and she and her relatives readily consented to have it performed.

Operation.—This was carried out at the Massachusetts General Hospital on Aug. 15, 1938, in precisely the same way as the others in this series of cases up to the point of the incision in the cord. Instead of a straight-pointed blade entered at the posterior aspect of the lateral column, a curved blade was employed

and entered at the point of attachment of the dentate ligament to the second segment. The curved point of the blade was turned upward and inward, with the idea of severing the fibers to the cervical segments and sparing those to the leg.

Course.—The operation was well borne, but it was not a success. Within four days the tremor occurred practically as before. There were slight spasticity of the left side and slight hemianalgesia of the right.

In view of the disappointing result, a second operation was suggested to the patient and was finally accepted.

Second Operation.—This was carried out on Sept. 28, 1939, at the Massachusetts General Hospital. The old wound was reopened without incident and an incision made in the cord a segment lower. This time, as in most of the previous cases, the Bard-Parker scalpel, no. 11, was inserted into the lateral column just below the posterior roots, to a depth of 4 mm., and swept out laterally to a point opposite the horizontal meridian. The extent of the incision was demonstrated to the staff by inserting the tip of an ordinary scalpel into it; the blood-stained area on the blade measured approximately 4 mm. on each side.

Course.—The patient made an uneventful recovery. She suffered severe flaccid paralysis of the left arm and leg. About the third week she began to move the leg, and about the seventh week the hand also. She could not, however, walk as far as before the operation or make use of the left hand, except to steady the right, which continued to show slight tremor. There was a mild intention tremor of the left hand, but only a trifling tremor of rest (fig. 15 *B*). On examination twelve weeks after operation, the strength of the hand was still improving. Spasticity of the leg was marked on flexion, and less marked on extension. There was moderate resistance to passive motion in both flexion and extension of the arm. The deep reflexes were all greatly exaggerated in the left arm and leg, with spreading. There was ankle, patellar, finger and wrist clonus. The Babinski, Hoffmann and similar reflexes were positive. The hypalgesia of the right side was unchanged.

The patient and her family are much pleased with the result of the operation. She is to begin to take belladonna, as medication was omitted after the operation. According to a report from the patient seven months after the second operation, the tremor has not reappeared and control is improving.

Case 6.—John G., a priest aged 35, referred by Dr. Harry Solomon, was admitted to the Boston City Hospital on Sept. 13, 1938. He had considered himself well until March 1933, when, without obvious cause, he began to have stiffness and weakness of the right leg. A diagnosis of "loose semilunar cartilage" was made, and the knee was operated on. During convalescence, tremor and weakness of the right arm, hand and leg appeared. These symptoms progressed in spite of administration of scopolamine and stramonium to the point of tolerance, until the patient was forced to give up his duties.

Examination showed a typical parkinsonian facies and oily skin. The right hand was held stiffly, with the fingers straight. There was a moderate tremor of rest, which was greatly exaggerated by intentional activity. The right leg was stiff. The gait showed typical propulsion. There was the usual loss of associated movements.

After due consideration, operation was accepted by the patient.

Operation.—This was carried out on Sept. 23, 1938. The procedure was substantially the same as that in the first operation in case 3. The right lateral pyramidal tract was incised at the second cervical segment to a depth of 4 mm., and the wound on the surface of the cord measured 3 mm.

Course.—There was less weakness of the arm than in the other cases. Strength was rapidly regained, and within two months the patient was walking alone and could use his hand with far less tremor. He returned to light duty. A period of overwork in December (three months after operation) was followed by severe weakness of the right leg, but practically no tremor. He was then treated with wine of Bulgarian belladonna and pilocarpine, under the supervision of Dr. Jerry Price. With rest and this medication there has been astonishing improvement for eight months, so that he is now able to walk readily alone and use his hand for writing, eating and dressing, and has regained many associated movements. Emotional tension or work brings on his symptoms to a certain extent.

Whether the improvement is to be attributed to operation, rest or medication is open to question. He had had an equally long rest before operation without improvement. The medication has done more for him than for any of the other patients in Dr. Price's series. It is possible that no one of these measures alone would suffice for him.

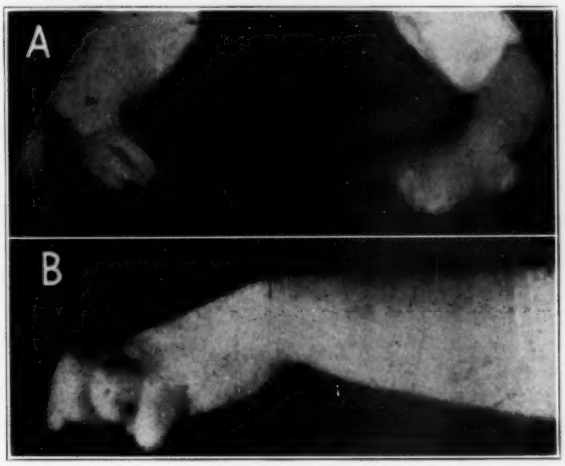

Fig. 16 (case 7).—*A*, before operation; note blur of the left hand. *B*, left hand after operation; note persistence of contraction. From a moving picture film; exposure, twenty-fifth second; background retouched.

From the foregoing review it is seen that partial section of the lateral pyramidal tract may be expected to produce partial relief of alternating tremor with little increase of weakness. After the experience gained in case 3, a complete section was carried out at the first operation in 2 additional cases.

Case 7.—Edith S., a housewife aged 49, was referred by Dr. Harry Solomon. She had considered herself well until 1918, when she had a severe attack of "influenza," with high fever and insomnia for several weeks. She recovered apparently completely and had no further difficulties until 1926, when she became depressed and there developed a slight tremor of the left side of the jaw, left arm and left leg. The tremor increased in severity and amplitude, and was accompanied by stiffness, weakness and pain in the shoulder. In 1938 she became con-

fined to her room, could get out of bed only with assistance, was in constant distress with pain in the arm and had difficulty in chewing or swallowing.

Examination on her admission to the Boston City Hospital on Sept. 3, 1938 revealed that she was obese, obviously in pain and miserable. The face was mask-like and seborrheic. The eyes were kept half closed. There was a constant tremor of the left side of the jaw. Saliva dripped steadily from the mouth.

There were a typical alternating tremor and intermittent rigidity not only in the jaw but in the left side of the neck, the left trapezius, deltoid and pectoral muscles and the left arm and leg. The tremor was of greatest amplitude in the arm, which was in such a violent continual movement that examination was difficult (fig. 16 *A*). The arm was stiff and weak. The hand was clawed, and movement at the shoulder and elbow was also limited. The patient complained

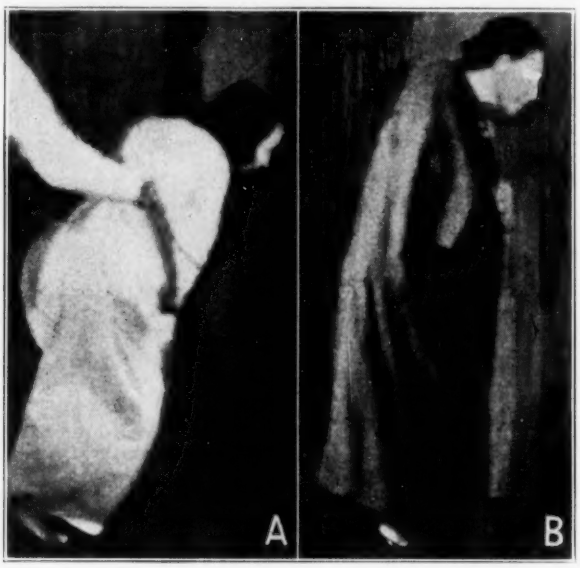

Fig. 17 (case 7).—Patient walking, (*A*) before and (*B*) after operation. Note characteristic propulsion in the preoperative photograph. From a moving picture film; background retouched.

of an aching, straining pain in the shoulder and of a tingling pain in the fingers. Extreme propulsion occurred on attempts at walking (fig. 17 *A*). The heart was slightly enlarged; general physical examination otherwise revealed nothing remarkable. There was slight cystitis.

The patient was treated with large doses of scopolamine hydrobromide, totaling as high as ⅓ grain (20 mg.) daily, with only slight relief. The addition of benzedrine was of no benefit, nor was the intravenous injection of 3 cc. of botulinus toxin. The possibility of operation, with its attendant difficulties and uncertainties, was explained to her and her family and the risks were willingly accepted.

Operation.—On Sept. 28, 1938, under anesthesia induced by avertin with amylene hydrate and ether, a cervical laminectomy was carried out, with little difficulty. The

third cervical segment was exposed on the left. A small longitudinal incision was made just lateral to the posterior root. The sharp-pointed Bard-Parker (no. 11) knife was inserted into it with the edge directed outward, the back being held at an angle of about 10 degrees from the vertical. It was thrust inward a distance of 5 mm. and swept directly outward, its point emerging about 1 mm. above the dentate ligament. The point of an ordinary scalpel was then inserted into the wound to demonstrate the size of the incision. The area of cross section which it occupied was found to be an approximately equilateral triangle, measuring 5 mm. on each side.

Course.—The patient made a good operative recovery and stated that she was more comfortable than at any time in the previous ten years. She made a fairly good convalescence, complicated only by the preexisting cystitis. At the time of discharge the tremor of the left arm and leg was absent at rest, and only a slight intention tremor developed on voluntary movement. Rigidity appeared to be decreased. She could bear weight on the leg and could walk somewhat better than before the operation. The hand was feeble, but its incapacity was chiefly due to arthritis of the fingers. She could move each of them separately, and could raise her hand to her mouth. There were no sensory disturbances. Her tolerance for scopolamine was reduced to approximately one tenth of her previous dose.

When reexamined in May 1939, the patient was found to have practically no tremor of the hand or leg (fig. 16 *B*). The tremor of the jaw and trapezius muscle continued unabated, but was far less annoying to her than before the operation. She had mild pains in the shoulder and fingers, which yielded to salicylates and heat. She was able to walk alone (fig. 17 *B*). The strength of the hand had improved. Rigidity was on the whole decreased as compared with the preoperative condition. The deep reflexes were definitely increased in the arm and leg, and the signs of Hoffmann, Babinski, Oppenheim and Mendel had appeared. In spite of the fact that she was confined to the house and unable to work, she considered herself greatly improved and was satisfied with the results of the operation. This situation is practically unchanged a year after operation. She has been given wine of belladonna with pilocarpine, without substantial additional benefit.

Case 8.—Ching Bin S., a Chinese man aged 44, was admitted to the Boston City Hospital on March 15, 1939. He had been well until six years before, when he had had high fever of brief duration, followed immediately by severe tremor of the right side of the jaw, right hand and right leg. The symptoms gradually increased, so that he became entirely incapacitated and could scarcely even take care of himself. He had been taking large doses of scopolamine, with only slight improvement.

He was miserable and poorly nourished. The results of examination were not remarkable, except for the presence of a rhythmic alternating tremor of the entire right side of the body, involving even the right side of the face, the right eyelid and the right side of the tongue. The jaw would close at regular intervals, with an audible click. The tremor of the hand (fig. 18 *B*) was most marked at rest and partly disappeared with intentional movement, so that he could write (fig. 19) or lift a glass with it.

The alternating rhythmic pattern was typical (fig. 18 *A*). There was a propulsive gait, with loss of associated movements.

The patient accepted operation, but not without hesitation.

Operation.—This was performed on March 30, 1939. The technic was precisely the same as that described in the preceding cases. The right lateral pyramidal tract was completely severed, from the posterior horn to the horizontal meridian, at the second cervical segment.

Course.—The patient made a fairly good recovery, but gained strength slowly. A little tremor appeared in the hand from time to time (18 *C*). The strength of

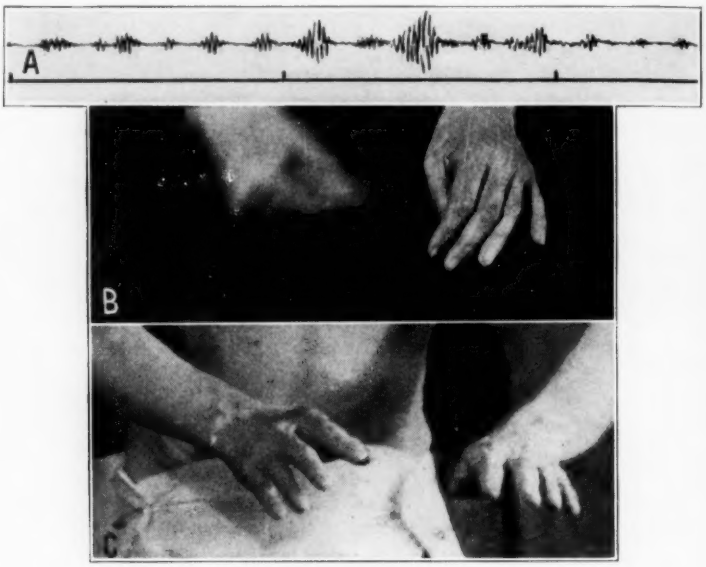

Fig. 18 (case 8).—*A*, electromyogram. Time in one second intervals. Below, patient's hands (*B*) before and (*C*) after operation. From moving picture film; exposure, one-sixteenth second.

Fig. 19 (case 8).—Patient's signature, before (above) and after (below) operation.

the hand increased, so that writing was improved (fig. 19). Walking was slightly better than before operation (fig. 20 *A*). Tremor of the face, jaw and tongue was unaffected. In spite of these benefits the patient complained that he did not feel well, but no particular difficulty was elicited. He was depressed and lost weight. He was discharged from the hospital on May 8, looking thin and wan.

On May 16 (about six weeks after the operation), word was received that he had suddenly vomited blood and died. Permission was obtained for an autopsy. It was observed that the stomach was greatly dilated and contained a little blood. No source for bleeding was disclosed. The operative wound was in good condition. The brain showed grossly the usual changes of presenile paralysis agitans. The lesion of the cord is shown in figure 21; there was typical descending degeneration of the lateral pyramidal tract, with no other important alterations.

The mechanism of death in case 8 remains obscure. It is hard to conceive that a lesion of the pyramidal tract would cause gastric stasis

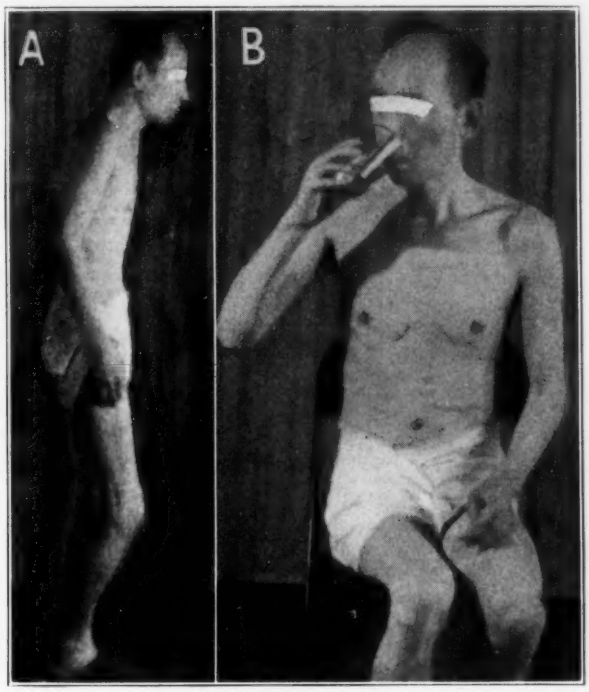

Fig. 20 (case 8).—Patient after operation, walking (*A*) and drinking from a glass of water (*B*). From moving picture film; background retouched.

or gastrostaxis. Pyloric hypertrophy and stenosis have been reported to result from the use of atropine.[27] The possibility of suicide by poisoning is to be considered.

COMMENT

The results of the surgical treatment of paralysis agitans permit a little further insight into the physiology of the disease. It appears

27. Brednow, W.: Einfluss hoher Atropindosen auf das morphologische und motorische Verhalten des Magens beim Enzephalitiker, Röntgenpraxis **7**:183-184, 1935.

now wholly unlikely that the alternating tremor is produced by release or stimulation of extrapyramidal fibers to the spinal cord, as postulated by Wilson.[28] The presumption is rather that the tremor is maintained by innervation of the pyramidal tract, since it is so substantially reduced by subtotal section of the tract. From the work of Klemme and from cases 1 and 2 of this series, it appears likely that the innervation reaches the pyramidal tract from one of the "premotor" areas. From the case of Pollock and Davis,[7] it appears that the timing and extent of the

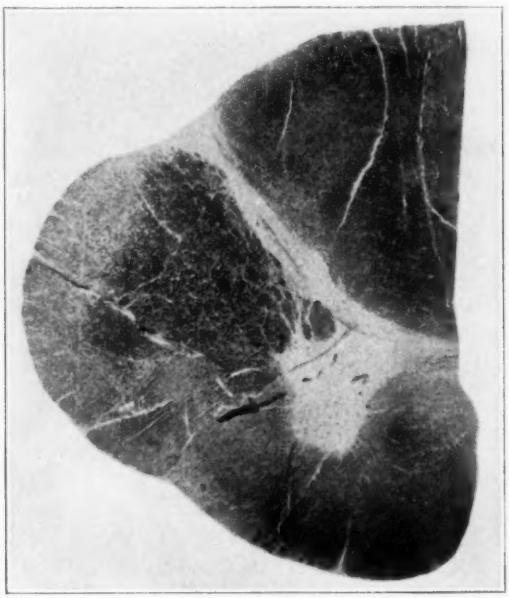

Fig. 21 (case 8).—Section from the fourth cervical segment of the spinal cord; Marchi stain. Stained granules are practically confined to the lateral pyramidal tract.

tremor may be dependent on a segmental reflex, and the similarity of electromyographic records of tremor to those of clonus is certainly striking.

Beyond these speculations one cannot at present go. The results of excision of the transitional or premotor cortex in cases 1 and 2 are surprising in view of the work of Aring and Fulton.[18] The production of increased reflexes and slight spasticity but of little disability by section of the lateral pyramidal tract in the spinal cord is in agreement

28. Wilson, S. A. K.: The Old Motor System and the New, in Modern Problems in Neurology, London, E. Arnold & Company, 1928, pp. 120-140.

more with the experimental work of Rothmann [26] and of Ranson and his co-workers [29] than with that of Tower.[30] This is perhaps because Tower's sections were more complete, being carried out in the pyramids of the medulla. Less weakness but more awkwardness were produced by resection of area 6.

From the practical therapeutic point of view it appears justifiable to conclude that operative treatment offers considerable hope of relief from severe unilateral tremor. Many problems of indication and technic remain, of course, to be solved. The first is, perhaps, that of the respective merits of the cortical operations and the chordotomies. This, in turn, rests on the question of how extensive the cortical extirpation must be. At present, the tentative conclusion seems justified that tremor can be relieved by a cortical operation which does not wholly sacrifice the Betz cell area, and should therefore interfere only moderately with the use of the extremity involved. If such is the case, a cortical operation is probably to be preferred when tremor of the face, neck or jaw is a serious consideration, or when the leg is not involved. Complete section of the lateral pyramidal tract is probably to be preferred if both the arm and the leg are severely affected. It apparently produced less disability than even a restricted cortical operation in most of the cases in this series. If the pyramidal fibers for the arm could be separated from those destined for the leg, the application of chordotomy could be widened.

A possible danger from cortical operations is the development of convulsions. One occurred during convalescence in case 2. A wise precaution might be to take electroencephalographic records before (and after) operation.

Treatment in cases of bilateral tremor has been undertaken apparently only by Klemme,[20] whose records would be a valuable contribution to the subject. The dangers of bilateral operation of either type are obvious, but the risk is perhaps justified in some instances.

The results of operation of either type on rigidity remain to be determined. Certainly, rigidity is not regularly produced by adding a lesion of the pyramidal tract to a parkinsonian tremor. This appears to vitiate the comparison often made between rigor and decerebrate rigidity. In 2 cases (cases 5 and 7) cited, mild rigidity appeared intermittently after section of the pyramidal tract. Perhaps modifications of Puusepp's or Davis' operation might be developed to meet the problem.

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29. Ranson, S. W.; Muir, J. C., and Zeiss, F. R.: Extensor Tonus After Spinal Cord Lesions in the Cat, J. Comp. Neurol. **54**:13-33, 1932.

30. Tower, S. S.: Pyramidal Lesion in Monkey, Tr. Am. Neurol. A. **64**:95-101, 1938.

SUMMARY

A review of the literature on the surgical treatment of alternating tremor is presented.

Eight new cases of unilateral tremor in which treatment was surgical are reported. Two of the patients had relief from tremor of one hand as a result of resection of the corresponding transitional cortex at the anterior edge of the Betz cell region.

The remaining 6 patients were treated by section of the lateral pyramidal tract. In 2 of the cases only a partial section of the pyramidal tract was performed; both patients obtained some improvement. In the 4 other cases the section was apparently complete, between the posterior horn and the horizontal meridian of the cord. All 4 patients experienced substantial relief, usually with distinctly less disability than results from extirpation of the precentral gyrus.

NOTE.—While this article has been in the printer's hands, 2 more patients have been operated on. One was a woman of 69, with a severe tremor of the right hand and leg. After section of the right lateral pyramidal tract the right hand became more useful than the left.

The other patient was a youth of 20, with a coarse, incapacitating tremor of the left arm and leg. The tremor was unaffected by removal of a large area of cortex anterior to area 6 and destruction of the head of the caudate nucleus. At a subsequent operation under local anesthesia, the incision was carried posteriorly into the anterior limb of the internal capsule; at this point the tremor ceased. The hemiparesis has largely cleared up, and no recurrence of tremor has occurred.

CORTICAL SOFTENING WITH ATROPHY OF INTERNAL CAPSULE AND DORSAL THALAMUS

CONNECTIONS OF VENTRAL LATERAL NUCLEUS OF THALAMUS

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We present the results of a microscopic study of a case of unilateral cortical softening in which the internal capsule and thalamic nuclei were completely atrophied on the left side. The condition was due to vascular occlusions. Among other things, the series shows clearly the four afferent pathways which enter the ventral posterior and ventral lateral nucleus of the thalamus, where they stand out in bold relief against a background barren of cells and of thalamocortical connections. These pathways and their serial connections with the ventral lateral and the ventral posterior nucleus are shown in figure 4 *B*. The work of Schuster [1] has given significance to the radiations of the brachium conjunctivum and to pallidal connections through the fasciculus thalamicus, or field H_1. The myelination of these tracts in brains of infants has been described by Környey.[2]

REPORT OF A CASE

Clinical History.—J. H. C., a distinguished teacher and scientist, died at the age of 78. Always a nervous, energetic, alert man, his previous history reveals nothing germane to the present study, except a tendency to stutter.

For several years the systolic blood pressure had ranged from 160 to 200 mm. Four and one-third years prior to his death he suffered an occlusion of the middle cerebral artery, resulting in right hemiplegia. Partial recovery followed, and for a year he could speak, walk and write his name. With repeated attacks the hemiplegia became complete, progressing through increasing indifference, somnolence

From the Department of Zoology, Cornell University.

1. Schuster, P.: Beiträge zur Pathologie des Thalamus opticus: I. Kasuistik, Arch. f. Psychiat. **105**:358-432, 1936; II. Gleichseitige Erweichung mehrerer Gefässgebiete, ibid. **105**:550-622, 1936.

2. Környey, S.: Zur Faseranatomie des Striatum, des Zwischen- und Mittelhirns auf Grund der Markreifung im der ersten drei Lebensmonaten, Ztschr. f. Anat. u. Entwcklngsgesch. **81**:620-632, 1926.

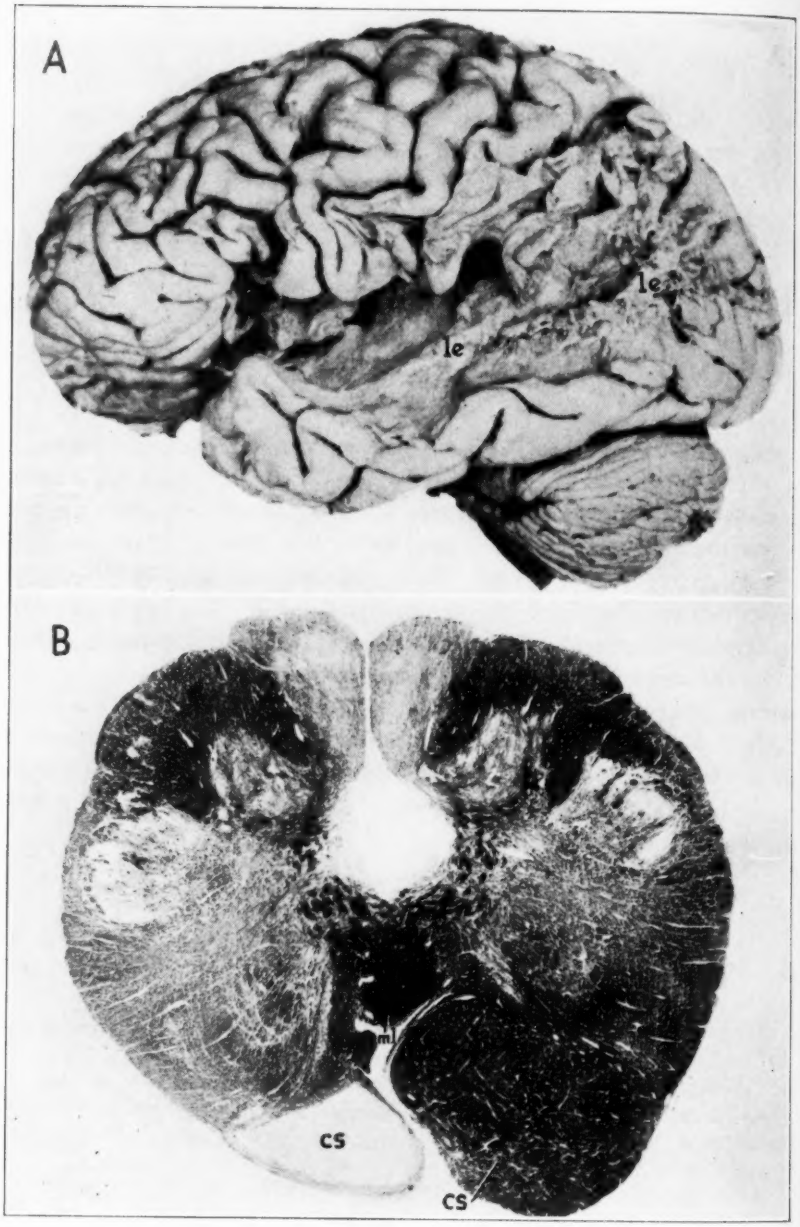

Figure 1

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and lethargy to profound aphasia, marked amnesia and right hemianopia. Sensory and motor functions of the right limbs and right side of the trunk were finally wholly lost; the face was not affected, except for slight diminution of sensibility; the general condition remained good; there was slight incontinence. Practically all disability was referable to cerebral and thalamic lesions.

Vision was retained in the left visual field but was largely defective in the right. Tests showed that the vascular occlusion in the brain affected reading as well as speaking of words. He understood what was said, recognized people, enjoyed listening to music, smoked many cigars and, for a bedridden paralytic, was generally fairly alert.

Speech, at first lost and then partially recovered, was entirely abolished during the last three years, except for an occasional involuntary "Goodbye" or "Yes," entirely unassociated with the slightest conscious effort to enunciate. Any such conscious effort early not only became a total failure but was such a pitifully painful psychologic experience that it was soon abandoned. Twice, however, on occasions two years apart, he spoke clearly and as intelligibly as in his well years. Once, when taken by surprise, he replied: "Oh, all right"; again, when completely absorbed in hearing a friend's account of his vacation, he asked: "Where is that lake?" He never talked in his sleep.

EXPLANATION OF FIGURE 1

A, left lateral view of the brain of J. H. C., showing the extent of the great cortical lesion in the parietal and temporal regions.

B, transverse section of the lower portion of the medulla oblongata of series J. H. C., showing the atrophy of the left corticospinal tract (*cs*) and reduction of the left half of the medulla oblongata. × 7.

In this figure and in the accompanying figures, the following abbreviations are used: *a*, anterior nucleus of thalamus; *ac*, acoustic radiations; *al*, ansa lenticularis; *am*, amygdala; *ar*, anterior thalamic radiations; *arc*, arcuate nucleus; *b*, temporopulvinar, or temporothalamic, bundle; *bc*, brachium conjunctivum; *cm*, central medial nucleus; *cr*, conjunctival radiation; *cs*, corticospinal tract; *d*, ventral supraoptic decussation; *dd*, dorsal supraoptic decussation; *f*, fornix; *fl*, fasciculus lenticularis; *fp*, frontopontile tract; *H*, prerubral tegmentum, or nucleus campi Foreli; H_1, fasciculus thalamicus; H_2, fasciculus lenticularis plus ansa lenticularis; *h*, hypothalamus; *hip*, hippocampus; *hp*, habenulopeduncular tract; *i*, intrathalamic bundle; *int*, internal capsule; *L*, lateral segment of red nucleus; *la*, nucleus lateralis anterior (dorsalis), or dorsal disseminate nucleus; *le*, lesion; *lg*, lateral geniculate nucleus; *M*, medial segment of red nucleus; *mb*, mamillary body; *mbf*, medial bundle of forebrain; *me*, medial nucleus of thalamus; *mg*, medial geniculate nucleus; *ml*, medial lemniscus; *mt*, mamillothalamic tract; *mv*, medial ventral nucleus; *nr*, red nucleus; *on*, oculomotor nucleus; *or*, optic radiation; *ot*, optic tract; *p*, pallidum; *pd*, dorsal portion of pulvinar; *ped*, basis pedunculi; *pl*, lateral portion of pulvinar; *pp*, parietopontile tract; *pr*, prerubral tract; *ps*, pallidosubthalamic tract; *pul*, pulvinar; *put*, putamen; *r*, reticular nucleus of thalamus; *ro*, rubro-oculomotor tract; *rro*, rubroreticulo-olivary pathway; *rs*, rubrospinal tract; *s*, strionigric fibers; *sn*, substantia nigra; *spt*, spinothalamic tract, or spinobulbothalamic tract; *st*, stria terminalis; *ste*, subthalamicotegmental tract; *su*, subthalamic nucleus; *sx*, subthalamic decussation; *t*, dorsal trigeminal tract; *tt*, trigeminothalamic tracts; *v*, pars ventralis of geniculate bodies; *va*, ventral anterior nucleus; *vl*, ventral lateral nucleus; *vp*, ventral posterior nucleus, and *vpl*, ventral posterior lateral nucleus.

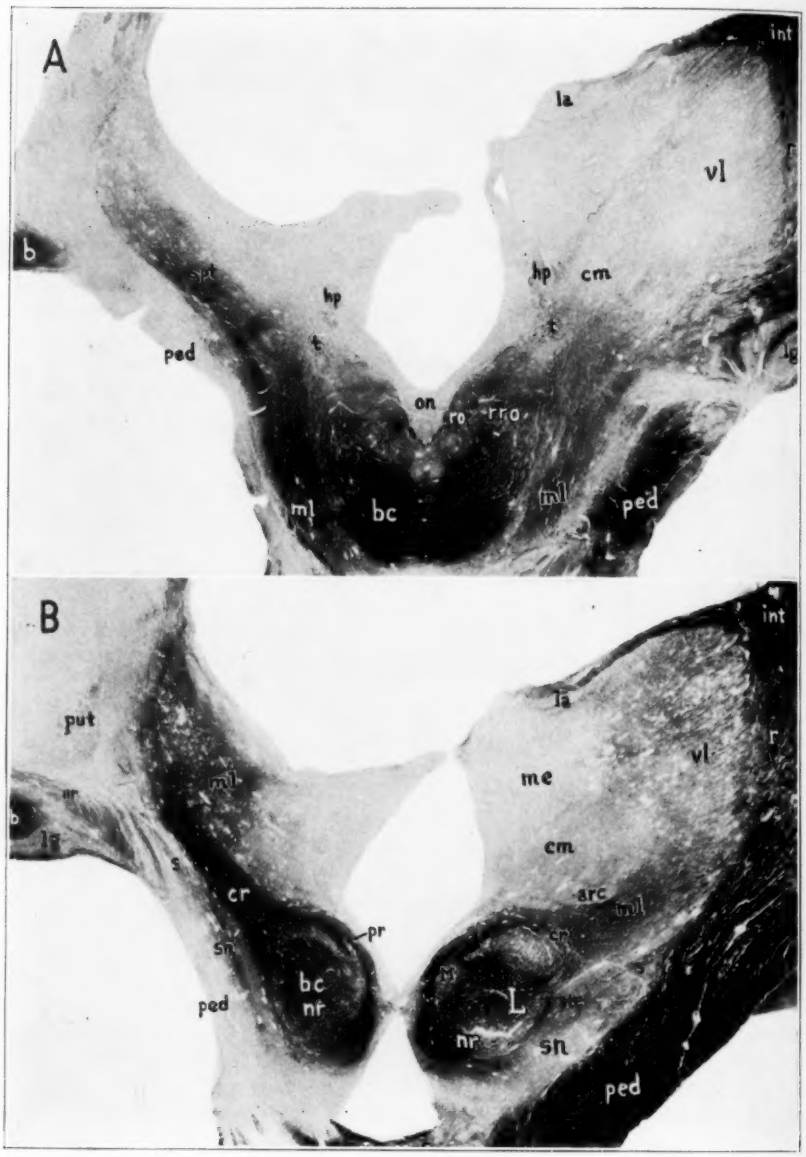

Figure 2

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Necropsy.—Postmortem evidence in the brain paralleled to a remarkable degree the clinical history, particularly as it related to the speech phenomena.

The brain showed a large softening of the lower parietal and upper temporal cortex on the left side, due to sclerotic occlusion of the left middle cerebral artery (fig. 1 *A*). The cortical softening resembled closely that in the case illustrated by Jelliffe and White.[3] Beneath the surface, the insula, claustrum, corpus striatum, internal capsule and most of the left thalamus were atrophied, as a result of occlusion of the left lenticulo-optic artery. What remained of the left lateral cortex was a shell, fairly well preserved but totally disconnected from the thalamus. The left gyrus cinguli was also disconnected from the anterior thalamic nuclei. The lower temporal and the hippocampal region were fairly well preserved. The cortex of the right hemisphere was atrophied, most severely in the prefrontal region.

The brain stem was removed and sectioned. Every tenth section was stained by the Weigert method and every alternate section with cresyl violet. The series includes 868 sections, prepared by Dr. W. R. Rundles.

Histologic Examination.—The hypothalamus and the supraoptic decussations were well preserved (fig. 3 *B, d, dd*). The nuclei tuberis laterales were distinct. The right mamillary body was pressed up into the third ventricle. The stems of both mamillothalamic tracts were myelinated to the point of bifurcation (fig. 3 *B, mt*), but beyond this point to the anterior thalamic nuclei were completely demyelinated (fig. 3 *A, mt*). We have noted such demyelination in several other brains of persons who had shown lethargy or somnolence. The fornix on both sides was normal. The hippocampi and amygdalae were fairly well preserved. The olfactory structures on the left side were compressed and atrophic. The medial bundle of the forebrain was distinct on the right side but reduced on the left.

The right dorsal thalamus had a large vascular lacuna (fig. 3 *A, le*) in the medial nucleus (fig. 2 *B, me*), and the dorsal lateral half of the thalamic radiation to the prefrontal cortex was sclerotic (fig. 3 *B, ar*). The adjoining part of the right frontopontile tract (fig. 3 *A, fp*) was demyelinated. Many small perivascular degenerations were evident in the right corpus striatum and, to a lesser extent, in

3. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, ed. 2, Philadelphia, Lea & Febiger, 1917, p. 881.

EXPLANATION OF FIGURE 2

A, transverse section through the posterior thalamic region of series J. H. C., showing complete atrophy of the left thalamus. On the left side the thalamic terminus of the spinobulbothalamic tract (*spt*) and the medial lemniscus (*ml*) end in a narrow area representing the atrophic ventral posterior nucleus. The temporothalamic bundle (*b*), coming from the amygdalar region, curved dorsally to enter the atrophic inferior portion of the pulvinar, situated farther back. × 2.4.

B, transverse section from series J. H. C. taken 5 mm. anterior to that in *A*, showing, on the left side, the independent termination of the brachium conjunctivum (*cr*) in the atrophic ventral lateral nucleus. Dorsal to it is the terminal neuropil of the spinobulbothalamic tract and the medial lemniscus (*ml*). Note the size of the left red nucleus (*nr*) and its fiber capsule (*pr*) from field H. × 2.4.

the right thalamus. However, general atrophy of the right thalamus and right corpus striatum was present.

The left optic tract (fig. 3 *A* and *B*, *ot*) was largely degenerated, the right only partially. The right geniculate nuclei were present (fig. 2 *A*, *lg*); those on the left side were almost wholly atrophic (fig. 2 *B*, *lg*). The lateral horn of the left lateral geniculate nucleus contained some cells which gave rise to a small contingent of the optic radiation (*or*).

The left internal capsule, composed of the thalamocortical, corticothalamic, corticotectal, corticonigric, corticopontile and corticospinal fibers, was entirely wanting; the basis pedunculi was sclerotic. From the red nucleus down to the lower level of the medulla oblongata, the left half of both the tegmentum and the reticular formation was reduced in size. The reduction was generalized and could be attributed to sclerosis of the cerebral peduncle and the corticospinal tract (fig. 1 *B*). Aside from the atrophy of the basis pedunculi and substantia nigra on the left side and a part of the frontopontile tract on the right, the structures of the brain stem from the red nucleus down to the cord were well preserved. The exception was the reduction in size of the left lateral tegmental nucleus of the midbrain, which receives the connections from the subthalamic nucleus and the substantia nigra. Both these structures were reduced on the left side.

The whole of the left dorsal thalamus was atrophied and devoid of cells. Only the terminal neuropil of the afferent tracts was present. The pulvinar and the medial and lateral geniculate nuclei were wholly absent. The course of the five tracts which enter the dorsal thalamus could be clearly followed. Their terminal neuropil was evident. Four of these tracts are of special interest since they entered the vestiges of the ventral posterior and ventral lateral nuclei. The reticular nucleus and the claustrum were completely destroyed with the insular cortex.

The spinobulbothalamic tract (fig. 2 *A*, *spt*) and the medial lemniscus (*ml*) together entered the ventral posterior nucleus, within which they formed an extensive area of neuropil devoid of nerve cells and other connections (fig. 2 *B*, *ml*). (Compare with this the normal ventral posterior nucleus shown in figure 4 *A*, *vp* and *arc*.)

At a higher level the radiations of the brachium conjunctivum (fig. 2 *B*, *bc*, *cr*) formed a prominent and distinct bundle, which entered the ventral lateral nucleus, ventral to the neuropil formed by the aforementioned sensory tracts (*ml*). The left red nucleus (*nr*) was well preserved, but was smaller than the right. The fibers (*pr*) which formed its anteromedial capsule, coming from field H, were not affected much by the thalamic atrophy. The cells of the prerubral field H, or nucleus campi Foreli, were well preserved. The tegmental decussation between the prerubral fields H was present, though reduced (fig. 3 *A*, *sx*).

In the left corpus striatum, the caudate nucleus and the putamen were completely destroyed; only a small part of the posterior end of the putamen was retained (fig. 2 *B*, *put*). Strionigric and corticonigric fibers were absent, and there was complete atrophy of the reticular portion of the substantia nigra (fig. 2 *B*, *sn*). The substantia nigra compacta was partly preserved. The left lateral tegmental nucleus of the midbrain was reduced, as was the upper part of the left central tegmental tract, especially its ventromedial component.

In the left pallidum, the frontal part of the lateral segment was absent. The medial segment was shrunken, with reduction of pallidal efferent fibers which extended down to the prerubral field H and into the subthalamic nucleus of Luys;

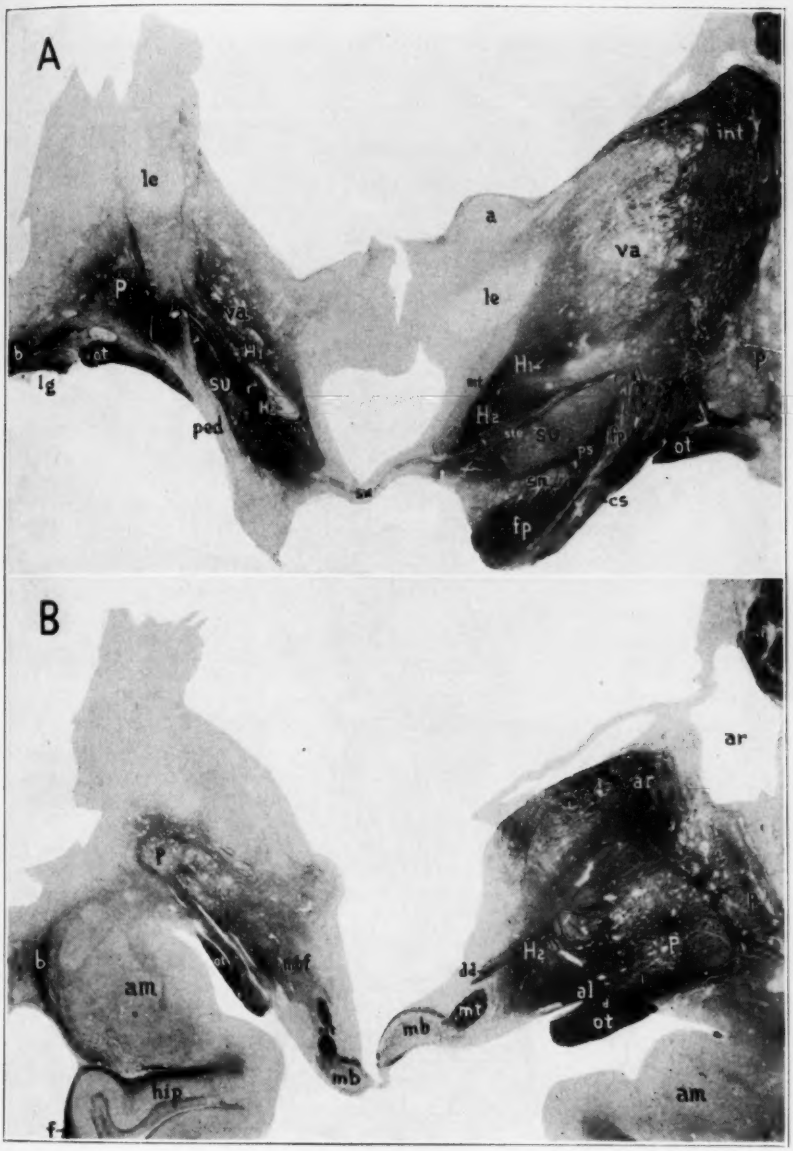

Fig. 3.—*A*, transverse section from series J. H. C. through the level of the subthalamic nucleus (*su*) and the fields H_2 and H_1. Note the demyelination of the mamillothalamic tracts (*mt*) and the large lacuna (*le*) in the right medial thalamic nucleus (fig. 2 *B*, *me*), from which arose the degenerated anterior thalamic radiation (*ar*) seen in figure 3 *B*. × 2.4.

B, transverse section from series J. H. C. through the level of the mamillary bodies and the anterior end of the thalamus, showing the large degeneration of the right anterior thalamic radiation (*ar*) on the right side, and total loss of the internal capsule on the left side. × 2.4.

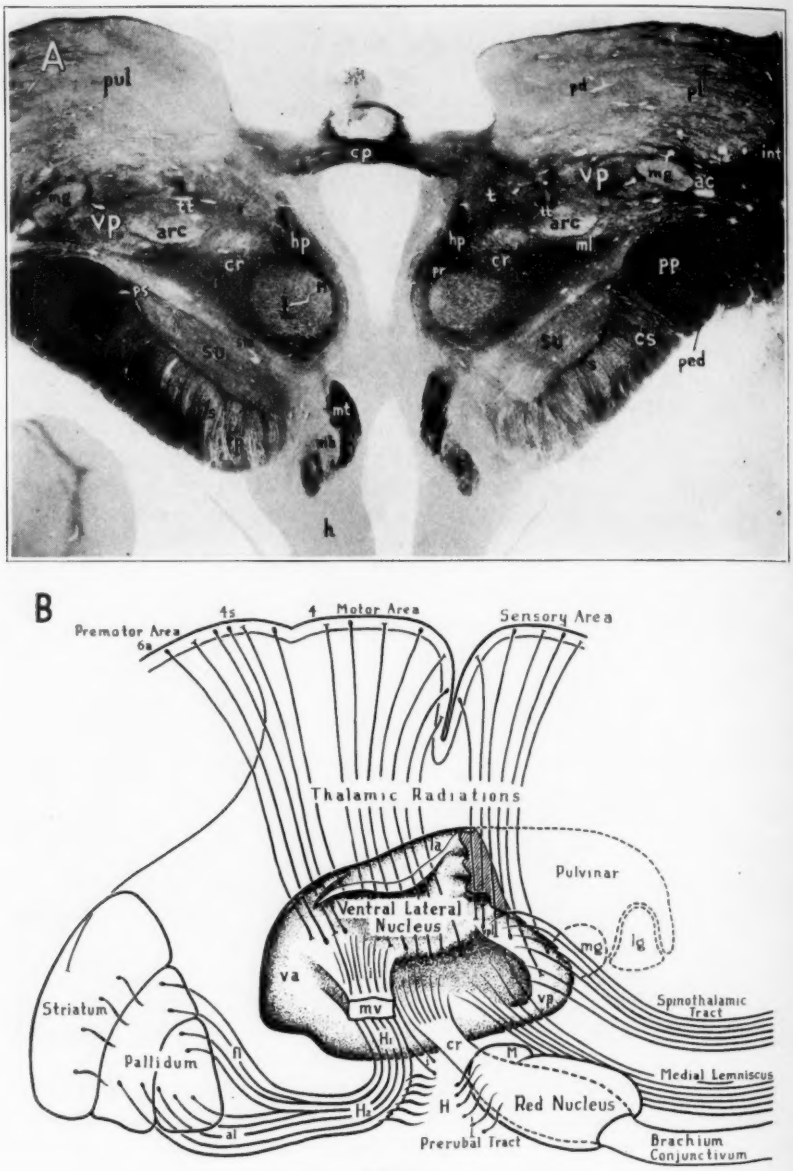

Figure 4

(See legend on opposite page)

the latter was atrophic but was filled with myelinated neuropil (fig. 3 *A, su*). A small subthalamicotegmental tract was present. There was a small fasciculus thalamicus, or field H_1, derived from field H_2. Field H_1 formed an area of neuropil in the medial portion of the ventral anterior nucleus of the thalamus (fig. 3 *A, va*). This neuropil was quite distinct from that formed by the brachium conjunctivum and from that formed by the medial lemniscus and the spinobulbothalamic tract at more caudal levels.[4] The fibers ventral to the red nucleus and the cupuliform formation were reduced on the left side.

The temporothalamic tract (figs. 2 and 3 *b*) is large in the human brain and connects the amygdala with the pulvinar.[5] In this case it was intact. Because of its great size in the human brain, it probably comes in part from the inferior temporal cortex. As seen in this series, a part of the bundle arose over the lateral surface of the amygdal, under the uncinate cortex (fig. 3 *B, b*). It then turned laterally and ran back under the pallidum and the internal capsule (figs. 2 *A* and *B* and 3 *A* and *B, b*). Its posterior end curved upward around the retrolenticular portion of the internal capsule and spread into the area of the atrophic inferior portion of the pulvinar. The polarity of the tract is fairly certain; it passes to the inferior part of the pulvinar, and it does not degenerate in the reverse direction. The inferior part of the pulvinar projects on the angular gyrus.

The left optic tract (figs. 2 *B* and 3 *A* and *B, ot*) was largely degenerated; the right one only partially. The right medial and lateral geniculate nuclei were present (fig. 2 *A, lg*); those on the left side were almost wholly atrophic (fig. 2 *B, lg*) except for a small part of the lateral horn. The cortical lesion (fig. 1 *A, le*) had completely destroyed the acoustic area and the acoustic radiations, as well as most of the optic radiations. This accounted for the degeneration of both the geniculate bodies on the left. Only a small contingent, which entered the lower

4. Papez, J. W., and Stotler, W. A.: Connections of the Red Nucleus, Arch. Neurol. & Psychiat. **44**:776-791 (Oct.) 1940.

5. Papez, J. W.: Connections of the Pulvinar, Arch. Neurol. & Psychiat. **41**:277-289 (Feb.) 1939.

EXPLANATION OF FIGURE 4

A, transverse section through the posterior end of the thalamus of a man blind from birth and devoid of the optic tracts. In other respects the thalamus is normal. It shows the cell clusters in the ventral posterior nucleus (*vp*), where the medial lemniscus (*ml*) and the spinobulbothalamic tract end. The trigeminothalamic tracts (*tt*) and the arcuate nucleus (*arc*) are also shown. Compare these normal structures with the deficits seen in figure 2 *A* and *B*, from the brain of J. H. C. × 2.4.

B, drawing of a reconstruction of the right ventral lateral nucleus of the thalamus, showing its contour, posterior and inner aspects. The connections of the spinothalamic tract, medial lemniscus, brachium conjunctivum, thalamic fasciculus (H_1) and the intrathalamic bundle (*i*) are indicated. The medial, medial ventral, central medial and arcuate nuclei have been removed from the concavity of the ventral lateral nucleus. The approximate positions of the pulvinar, red nucleus, medial geniculate (*mg*) and lateral geniculate (*lg*) nuclei are shown in dotted outline. The two way thalamocortical connections with the sensorimotor area are also shown.

part of the optic radiation, appeared on the left side (fig. 2 *B, or*). It probably came from the lateral horn of the lateral geniculate body, which contained some nerve cells.

The left occipital lobe, including the visual striate area, was sectioned, and alternate sections were stained for fibers and for cell content of the cortex. The optic radiations were completely degenerated, and layer IVc of the striate cortex showed marked loss of neuropil. The stria of Gennari and Vicq d'Azyr had not degenerated with the optic radiations. It was fairly well preserved, and so was the striatum calcarium.

The obvious inference is that the optic radiations do not contribute to the bulk of the stria, which seems to be more closely related to the stratum calcarinum.[6] The stria and the stratum calcarinum appear to form a local association system for the visual striate area as a whole. The primary visual pattern of fibers from the retina to the lateral geniculate body[7] and then to the visual striate area[8] is probably a point for point projection system which governs the focus of the excitation pattern in the visual striate area. From the associative nature of the stria of Gennari and Vicq d'Azyr, it is inferred that the focal excitation is further spread through the entire visual striate area, and is then irradiated into the surrounding parastriate and peristriate areas of the cortex.[5]

Attention is here called to the concentric structure of the retina and to the concentric arrangement of the laminas of the lateral geniculate nucleus and of the striate, parastriate and peristriate areas of the cortex. Such elaborate concentric architecture does not exist in any of the other receptor-cortical systems. It seems that this concentric arrangement may have a special significance in governing the cortical visual process. This in its totality must be a concentric process with dimensional attributes. Here, a mechanism for representation of form is strongly suggested.

COMMENT

In a case of complete unilateral atrophy of the thalamus due to vascular occlusion, which produced destruction of the cortex and of the internal capsule, we have shown that five major afferent pathways end in the ventral posterior and ventral lateral nucleus of the thalamus. These pathways are the spinobulbothalamic tract, conducting cutaneous sensibility; the medial lemniscus, conducting proprioceptive sensibility; the brachium conjunctivum, conducting cerebellar discharge; the fascic-

6. Rundles, R. W., and Papez, J. W.: Fiber and Cellular Degeneration Following Temporal Lobectomy in the Monkey, J. Comp. Neurol. **68**:267-296, 1938.

7. Brouwer, B., and Zeeman, W. P. C.: The Projection of the Retina in the Primary Optic Neuron in Monkeys, Brain **49**:1-35, 1926.

8. Poliak, S.: The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932.

ulus thalamicus, or field H_1, conducting pallidal discharge, and the intrathalamic fasciculus. Discharges along all five of these pathways find their way to the sensorimotor cortex.

In order to show how these afferent paths enter the nucleus in a linear order, we have reconstructed the nucleus from serial sections of a nearly normal brain and have shown its connections with the five afferent pathways (fig. 4 *B*). An inspection of the figure will make evident these connections.

A section through the posterior end of a normal ventral posterior nucleus (fig. 4 *A, vp*) shows the clusters of cells and neuropil which mark the entrance and dispersion of the medial lemniscus (*ml*) and the spinobulbothalamic tract. The cluster formation (*vp*) is conspicuous in the human brain and may indicate memberment or somatotopic representation.[9] There are wide overlapping and blending of proprioceptive and cutaneous terminals in this region.[10] This ventral posterior nucleus in the thalamic region has connections passing to and from the upper and middle portions of the postcentral cortex.[8] More medial is the arcuate nucleus (arc), which receives the trigeminothalamic tracts (*tt*).[9] The arcuate nucleus is connected with the lower part of the postcentral cortex.[11] This, again, is a two way connection.

The conjunctival radiations (fig. 4 *B, cr*) form a pennant of fibers pointing laterally from the frontal end of the red nucleus. Their course is under the arcuate nucleus, but their actual ending is in the ventral border of the ventral lateral nucleus some distance anterior to the medial lemniscus.[12] The conjunctival radiations are close to field H_1, but in a more lateral position. Farther back there is a small radiation of the brachium conjunctivum to the central medial nucleus.

Much of field H_2 ends in the subthalamic nucleus of Luys and in the prerubral field H, before H_1 is given off. The field *H* is a special link which connects H_2 (hence the pallidum) with the red nucleus.

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9. Walker, E. A.: The Primate Thalamus, Chicago, University of Chicago Press, 1938. Crouch, R. L.: The Afferent Fibers of the Thalamus of Macacus Rhesus, J. Comp. Neurol. **72**:77-186, 1940.

10. Dusser de Barenne, J. G., and Sager, O.: Ueber die sensiblen Functionen des Thalamus opticus der Katze, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:231-272, 1931. Dusser de Barenne, J. G., and McCulloch, W. S.: The Direct Functional Interrelation of Sensory Cortex and Optic Thalamus, J. Neurophysiol. **1**:176-186, 1938.

11. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, A. Research Nerv. & Ment. Dis., Proc. (1934) **15**:274-288, 1935. Dusser de Barenne, J. G., and McCulloch, W. S.: Sensorimotor Cortex, Nucleus Caudatus and Thalamus Opticus, J. Neurophysiol. **1**:364-377, 1938.

12. Ranson, S. W., and Ingram, W. R.: The Diencephalic Course and Terminus of the Medial Lemniscus and the Brachium Conjunctivum, J. Comp. Neurol. **56**: 257-275, 1932.

Field H_1 is a special terminal which ends in the ventral lateral nucleus of the thalamus, well in front of the conjunctival radiations and to their medial side.[2] In addition, there is a large intrathalamic fasciculus (*i*), which enters the ventral lateral nucleus dorsal to and in front of field H_1. It seems to come from the medial ventral nucleus or from the front of the central medial nucleus.[13]

The ventral posterior nucleus may be regarded as the sensory nucleus, and the ventral lateral nucleus as the association nucleus, for the sensorimotor apparatus.[14] Lesions of the nuclei show that their functions deal with bodily cognizance, as well as with motor functions, and with perceptions of muscular movements, stresses and strains (gleidokinesis).

Schuster has shown that lesions of different parts of the ventral posterior and ventral lateral nuclei are associated with various kinds of sensory, perceptual and motor disturbances.[15] The sensory disturbances are usually from lesions in the ventral posterior nucleus. The pain syndrome, or hyperpathy, occurs when the lesions are in the lateral part of the lateral nucleus, close to the reticular nucleus. The pain syndrome contributes to the illusory and fantom-like disturbances of the body schema. Anosognosia, or perceptual disorder of the body schema, usually accompanies hyperpathy and appears in association with thalamic lesions, especially those of the right side, which interfere with the connections of the thalamic nuclei related to the sensorimotor cortex and the parietal lobe.

According to Schuster, the motor disturbances are of several varieties: tremor-like movements, choreoathetosis, the thalamic hand and disintegration of voluntary movements. The tremor-like movements which appear with volition are due to the interruption of rubrothalamic connections (*cr*). Choreoathetosis is due to a break in the pallidothalamic connections (field H_1). The thalamic hand is always associated with choreoathetosis and with a remnant of voluntary function. Extensive lesions of the lateral nucleus are observed with complete disintegration of voluntary movement and hemiplegia. Schuster concluded that the thalamocortical system is an essential part of an integrated cortical and subcortical apparatus which governs the activities

13. Papez, J. W.: Thalamic Connections of a Hemidecorticate Dog, J. Comp. Neurol. **69**:103-120, 1938.

14. Papez, J. W.: Comparative Anatomy of the Primary or Sensory, and the Secondary or Cortical Nuclei of the Thalamus, Anat. Rec. **76** (supp.):72-73, 1940.

15. Schuster, P.: Beiträge zur Pathologie des Thalamus opticus: III. Beziehung der Sensibilitätstörungen und der anosognostischen Störungen zu den thalamischen Herden, Arch. f. Psychiat. **106**:13-53, 1936; IV. Motorische Störungen, ibid. **106**: 201-233, 1937.

of the muscular system. It is apparent that the activities of this apparatus deal with the construction of the body schema, which parallels sensorimotor development.[16]

The thalamic radiations between the ventral lateral nucleus and the precentral cortex are dense and extensive. For the reasons given by Schuster, the nucleus is a significant component of the dorsal thalamus for the control of voluntary activity. The cerebral connections of this nucleus are mainly with the motor and premotor areas. From these areas there is also reversal of innervation through corticothalamic fibers to the same nucleus.[17] This reversal of innervation is a general characteristic of all areas of the cortex, except parts of the temporal lobe. In case of the ventral lateral nucleus it is especially widespread, involving large areas of the cortex, as well as an extended mass of thalamic tissue. The long anteroposterior dimension and the thickness in lateral extent of the nucleus and its numerous fiber bundles can be accounted for by the great extent of the cortical area with which they are united by this two way system of fibers. The physiologic evidence on this two way relation of the sensorimotor cortex and the ventral posterior and ventral lateral thalamic nuclei gives this apparatus a dynamic significance.[11]

In the sensorimotor cortex the afferent processes representing bodily and external stimuli coming through the ventral posterior nucleus are combined with the subcortical processes from cerebellar and pallidal sources coming through the ventral lateral nucleus. The cortex gives origin to a series of descending pathways: the parietopontocerebellar pathway, the corticonigric tract, the corticotegmental tract, the corticobulbar and corticospinal tracts, the frontopontocerebellar pathway and the corticostriate (or subcallosal) bundle. Presumably, each of these tracts is subject to progressive discharge during motor activity.

The two way innervation which exists between the thalamic nuclei and the sensorimotor region may be viewed as a dynamic device for governing the flow of impulses along these tracts which facilitate, release, energize, inhibit or otherwise contribute to the regulation of movement. Such a device could regulate the march of movement in the cortex. In a similar way, the integration of the body schema may take place between the sensorimotor region and the parietal cortex.

16. Schilder, P.: The Image and Appearance of the Human Body, in Psyche Monographs, London, Kegan Paul, Trench, Trubner & Company, Ltd., 1935, no. 4.

17. Sachs, E.: On the Structure and Functional Relations of the Optic Thalamus, Brain **32**:95-186, 1909.

IMPULSIONS

A SPECIFIC DISORDER OF THE BEHAVIOR OF CHILDREN

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Human beings have interests toward which they retain a varying degree of freedom. They may be preoccupied with specific thoughts and ideas; they may be specifically interested in the one or the other group of objects or data. These interests may appear to be theoretic. A person may, for instance, have a great interest in railroads, pictures, landscapes, clothes or flowers. However, such an interest never remains in the sphere of contemplation alone. It sooner or later leads to actions. The person interested in landscapes will have to travel in order to see them or at least have to go to places where painting and pictures are exhibited, or he may have to paint and photograph them himself. The person interested in technical problems will sooner or later start to construct, or at least to collect. Interests of this type may be worth while and may mean the lifework or the life interest. One is inclined to believe that persons should have such an overwhelming preoccupation with their work. However, it is understandable if a man does not live out these impulses in his professional life but enjoys some hobbies or collecting in his private life. It might sometimes be difficult to decide which of these interests are commendable and which are not.

At present, however, the interest is in the direction of flow of the impulses of an individual person. He may be more occupied with sex than the average person, or he may collect stamps. He may be a gambler and feel that his life interest centers around the card table, or he may think that he should do nothing but hoard money. He may not only wish to do so but feel completely justified in his attitude. It has been learned that persons who have neurotic symptoms show also definite trends in their impulses; in other words, definite character trends are found to be connected with neurotic symptoms. Character trends and neurotic symptoms differ from each other so far as a man fights against the neurotic symptoms and suffers from them, but accepts his character trends. In other words, the neurotic symptoms are rejected by the ego, in the psychoanalytic sense, and cause suffering, while the person suffers

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from his character only to the extent that society punishes him. These facts are well known in psychoanalysis. According to Fenichel,[1] the obsessional character is always an anal character. Following the concept of Freud and Abraham, he mentioned stubbornness, defiance, orderliness and parsimoniousness as basic features. Anal characters are pedantic and punctual; they have a tendency to collect and to enjoy possessions. Winterstein[2] similarly has written an interesting study on collecting.

We have made a series of clinical observations on children which seem to lead to a deeper understanding of these problems.

Billy, a boy aged 5, showed an overwhelming interest in doors and door checks, so that it was almost impossible to remove him from doors. He looked at them, played with them and was so preoccupied with them that one needed force to get him away from them. He was severely impaired in his social functioning. Larry was interested in numbers. He wrote down a long series of numbers and was preoccupied with counting. Before coming to the hospital he had been running for hours in the streets noting the house numbers. He wanted to explore the longest streets in New York.

After having studied outspoken disorders (cases 3 and 4), we became aware that similar behavior in children is by no means rare. We saw children who were preoccupied with drawings of sexual content, others who were preoccupied with drawing of animals. They enjoyed their activities and interests, although from time to time they became aware that they were helpless to prevent them. The chief difficulties arose from the fact that their behavior led to a conflict with the surroundings. Casually, these preoccupations might be referred to as obsessions and compulsions. The children, however, felt that they had an interesting and fascinating occupation and regretted merely the lack of understanding of adults. We propose the term "impulsions" for these preoccupations and activities.[3] They do not represent merely a passing or fleeting impulse which suddenly breaks through the defenses and fears on the surface; they are preoccupations and actions which are in the foreground of the person's experience for weeks, months or even years. Impulsions are not obsessions in the strict sense. They have something in common with the obsessive character trends. It seems

1. Fenichel, O.: Clinical Psychoanalysis, New York, W. W. Norton & Company, Inc., 1934.

2. Winterstein, A.: Der Sammler, Imago **7**:180-194, 1921.

3. The term "impulsion" has been used in a similar sense by John Dewey (Art as Experience, New York, Minton Balch & Company, 1934). J. C. Whitehorn (Concerning Emotion as Impulsion and Instinct as Orientation, Am. J. Psychiat. **11**:1093-1118 [May] 1932) calls impulsion the signal of a biologic need and distress leading to action. H. A. Murray (Exploration in Personality, New York, Oxford University Press, 1938) spoke of impulsion as the tendency to respond quickly and without reflection. This use of the word differs from that of Dewey and Whitehorn. We use the term to characterize a clinical entity.

worth while, therefore, to start the discussion with the report of a case in which impulsions and obsessions were present at the same time.

REPORT OF CASES

CASE 1.—Marvin came for treatment to the mental hygiene clinic of Bellevue Hospital when he was about 12. He was a tall, rather poorly nourished boy of Jewish descent. He complained about obsessions and compulsions. When he crossed the street he had to hit one leg with the other four times, otherwise he feared that he might be hurt or killed while crossing. Furthermore, he was afraid that somebody might touch him on the street and kill him by this very touch. Later we learned that he had a vague idea that he might acquire tuberculosis by the touch. The obsession had become so severe that he stopped crossing streets and would not go to school. These obsessions developed after he had heard his mother tell how interesting life in a Polish village in Europe might be. He had wished urgently to go there and to participate in all the fun. This thought had reached an overwhelming intensity, and he finally decided not to think of it any more. But he found this impossible. Finally he threatened himself with death if he did not stop, and started to kick himself in the shins. Even that was not successful, and from then he feared he might die while crossing the street.

His early history revealed a great amount of aggressiveness. With a group of boy friends he enjoyed catching cats, tying them and torturing them to death. Once they also tied another boy. However, the patient said he disapproved of this. He finally gave up torturing cats, after he had a nightmare in which an enormous cat sat on his chest. When treatment began he was at the beginning of puberty. There had always been great sexual curiosity concerning his sister and his mother. His attachment to his mother was close; he was afraid of his father. He had a brother about eight years older than himself, who had been considered schizophrenic. However, in our opinion, the brother was not schizophrenic, but suffered from complicated aggressive impulses. The whole family was a rather violent one. The father and mother fought incessantly and threatened violence to each other and to the children. The children had outbursts of hate against each other; the patient himself had once threatened his sister with a knife. There cannot be much doubt that aggressive impulses were of enormous importance in this case. However, characteristically, the picture started with an unfulfiled wish. The boy obviously felt that his wishes should not be denied him; they were of enormous urgency. "I hit myself in school in order to forget a desire to go to Europe. I hit myself four times on the left arm with the right arm and said to myself: 'If I don't forget I should get killed.' I know I don't want to die, and I figured by threatening myself with death I could conquer the power that gains control over my reason." He hit himself on another occasion. "Only when I fought with a guy and hit him hard and I felt it was too much, I said: 'I hit myself now so that you get even with me.'" He was obviously afraid of the strength of his own impulses, especially the aggressive ones. He did not have power to deny himself any wishes. He liked to hitchhike on trolley cars; he liked to go fishing, although he knew that it was against the law. He was very unhappy when he did not get immediately whatever he wanted. He usually succeeded in securing, either from his older brother or from his mother, the fulfilment of most of his wishes. In this way he acquired a book on jujitsu, a bicycle, money to join the "naval reserve" and, finally, a bayonet. Under treatment he gained insight and lost his symptoms; however, the urgency of his wishes remained. He still often asked his mother one question several times, preferably four.

Since the age of 4 he had been interested in death, owing partially to the influence of his brother, who was continuously preoccupied with death and murder. "I used to think what would happen if my mother died." He thought also of the death of his father when the latter went to a hospital for an operation. His father and mother were both aggressive toward him; they hit him repeatedly. The mother, in addition, was much attached to her children and tried to make them as dependent on her as possible. He was in continuous fights with his sister. He was also interested in seeing her undress. He began to masturbate at 10 years of age, two years before he came for treatment; emissions started at this time, which made him feel weak and scared.

The treatment lasted from December 1936 to June 1937, with good results. In April 1938 he occasionally complained and asked his friend three or four times not to forget to call him when he went fishing. His dreams were still of the following type: "One of my friends was run over by a subway train. He would like to have a gun to shoot rats."

In the middle of May 1938 he broke his arm while jumping from a trolley car on which he was hitchhiking. He was aware of the danger of hitchhiking on trolley cars, but he could not resist the impulse. The healing of the fracture was uneventful, but he became preoccupied with hypochondriacal ideas—for instance, that his arm was weak, that there was a red mark and that the veins "stuck out." He felt like a cripple; he wished that everybody else would have a broken arm. His apprehensions expressed themselves in dreams. He worried also that his breasts were too large and that his hand might fall off at the red line. However, these symptoms disappeared after he had realized that his fears were punishment for his aggression. In September 1938 he wanted to kill people who pushed him in a crowded subway. He bought a gun to compensate for his weakened left arm and felt then that nobody would touch him. Early in 1938, at the age of 14, he had his first sex relations with a prostitute. He felt that he would like to go to a prostitute every day. He showed his penis to a woman looking out of a window. The family and he decided that he should be sent for a while to an institution (Pleasantville, N. Y.). When this was decided he demanded of the physician that it should be done immediately. Meanwhile, he and some friends broke open a box in the hope of finding candy and money. He had continuous fights at home. He said he would like to kill his teacher, who had a grudge against him, or run over him with a car. He finally was placed in an institution, but he soon felt that he had to go home again and ran away repeatedly; he was discharged. In April 1939 he complained only of his strong sex urge. In December 1939 he was fairly well adapted, but his dreams were of the following type: "There was war in this country, and they gave everybody a revolver in school. They gave me a .38 revolver. I felt very happy. Maybe I want a girl more than a gun."

This patient had very strong desires. He wanted to have his wishes fulfilled, and this immediately. He wanted also to be reassured that his wishes would be fulfilled; his tendency to repetition was partially due to this. He could not stand disappointments. His wishes were chiefly, though not all, of an aggressive type. He wished, for instance, to go to Europe and to play with other children. There were likewise frankly sexual wishes. It was probable, however, that even the wishes which were not frankly aggressive had an aggressive element. He tried to

keep himself away from these wishes by threatening destruction to himself. His wishes led him to actions which were more or less dangerous, such as hitchhiking and fishing in forbidden waters. Once such a wish had occurred he was completely preoccupied with it and did everything to fulfil it. He felt that he should be punished; when he finally broke his arm while hitchhiking he said that he deserved it. One can only surmise the psychogenesis of these impulsions. One suspects that he felt spoiled, on the one hand, and threatened, on the other hand. He reacted with a wish to kill, for which he felt that he deserved punishment. This case shows particularly clearly the relation of impulsions to compulsions and obsessions. It also offers elucidation of the psychology of accidents and shows the close relation between hypochondriacal ideas and the fear of punishment.

CASE 2.—Stanley, aged 9, was examined first on Nov. 1, 1937, in the mental hygiene clinic. He was under observation in the children's ward in November 1938. In a Stanford-Binet intelligence test made in the clinic his intelligence quotient was 104. According to the reports of teachers and agencies, it was impossible to discipline him. He went to movies once or twice a day, broke things—especially mirrors—and tore his mother's clothes off her body. He also liked to use cosmetics and to wear his mother's clothes. He was inclined to show feminine mannerisms. The agency had tried to hospitalize him since his first contact with the clinic, but the mother did not cooperate until forced to by the Child Welfare Agency. She consistently denied that there was any problem. Her only complaint was that he was not 100 per cent boyish. In the ward he was restless and fidgety. He did not have much contact with other boys. He could not stick to any occupation. He made an effeminate impression, and other boys called him "sissy." He sat and daydreamed, and did not do his school work. He showed no evident anxiety or any capacity for making attachments. He seemed completely preoccupied with his daydreams, except when he was drawing pictures of girls, mostly in vivid colors, with large heads and rather elaborate dresses. Sometimes the breasts were particularly marked. It was almost impossible for him to draw a man. Finally, when he was persuaded to do so, he also immediately drew a girl and asked: "Can't I draw a lady too?" ("Why do you want to?") "I can't help it." He stated that all women and all men have testes and a penis—this in spite of the fact that the year before he had said in the clinic: "I would die if my penis would be cut off, but I would look just like a girl then. . . . Only women have babies; I don't know why." He volunteered the information that his testes were "up" and that then they descended. He asked the examiner why his body looked like that of a girl. "See, my waist comes in like a girl. The fellows say so. It should be straight." He said that he slept in the same bed with his mother because when he was alone he was afraid of "spooks." With regard to his earliest memory, he said: "My mother was in the bathroom, and I went in and she shut the door on my finger; it hurt. That was before my daddy went away." At the age of 6½ he dreamed that he shot his father because he hit his mother. "I shot him through the heart; he was dead and I was scared. I awoke feeling scared because I thought I had shot my father."

Stanley's father suffered from tuberculosis for many years. From infancy until April 1937, Stanley was boarded with private families and in a boarding school.

In the boarding school he had an accident, and the mother said that he had changed afterward. The mother was an aggressive, suspicious person, who believed she had clairvoyant powers. She expressed devotion to the boy.

When the boy first came to the clinic he had undescended testes; he was short and obese, with a girdle type of fat distribution. His hands and feet were soft, small and infantile in configuration. His muscles were flabby.

This boy was preoccupied with the problem of masculinity and femininity. He seemed to have a fundamental doubt concerning his masculinity, partially based on the fact that his testes were undescended. His idea that women also have testes and a penis, although smaller, showed his deep reluctance to acknowledge that human beings exist without testes. That one deals indeed with a compensatory mechanism is proved by the fact that the boy previously acknowledged that girls have different sex organs. He appeared to be resigned to play the role of a girl and paraded before the mirror in the dresses of his mother. He drew pictures of women in an impulsive way. His pictures usually showed long hair, a large mouth and crude and unfinished bodies. In some drawings the breasts were emphasized. His drawings tended to become more and more schematic and distorted. At the same time he showed a deep attachment to his mother and a tendency to identify himself with her, and strong hostility against his father. He said that he could not draw a picture of a man. His first memory was that his father did not want to have him home, and the first dream he could remember was that he shot his father. He showed no manifest anxiety, although he spoke often of being afraid. The impulse was here directed toward expression in drawing of a specific topic which was closely connected with his fundamental problems. There is no question that his drawings did not express his problems directly. One does not expect impulsions to be direct expressions of drives. Also, in the light of case 1, it is clear that many of the patient's impulsions had a more or less symbolic character. In this respect they were not different from compulsions.

Although in both case 1 and 2 the impulsions played an important part, they did not dominate the picture as completely as in Billy's case (case 3).

Case 3.—The case of Billy has been studied extensively, and parts of his history are to be found in the book by one of us (L. B.).[4] The case is also discussed by Bender and Woltman.[5] Billy was 5½ years of age when he was first admitted to the children's ward of Bellevue Hospital. He was a boy of superior intelligence, the only child of parents with college training. His home life had not always been satisfactory, as his parents had not been entirely compatible. Several times the mother had gone home with Billy because of jealousy, sexual incompatibility or a so-called nervous breakdown. The birth was difficult, since the

4. Bender, L.: A Visual Motor Gestalt Test and Its Clinical Use, Research Monograph 3, American Orthopsychiatric Association, New York, 1938.

5. Bender, L., and Woltman, A.: On Puppetry, to be published.

mother had a narrow pelvis, and instruments were needed. It is probable that Billy had heard this discussed in his presence. There was no evidence, however, that his head was injured at the time of birth. He was born with an imperforate anus, which was operated on the second day after birth. The function of the anal sphincter was impaired, and he had to have dilatations of the anus, by his mother's finger almost daily and by physicians' instruments from time to time, until the age of 2, and at intervals thereafter. The normal course of his oedipus complex was interfered with because of the relationship between the mother and father and the frequent visits of the mother and child away from home. He openly expressed a hatred of the father, the desire for his death or removal from the home and the wish to have the mother to himself. He identified himself so much with his mother that he expressed a strong dislike for his penis. He wished to be like his mother. He wanted to sit down to urinate; he often denied having a penis. At the age of 2½ years, when he was visiting with his mother in the home of his grandparents, he enjoyed the pleasure of automobile rides. He was fascinated by the stop and go lights and seemed to believe that they made the cars stop and go. At this time at home he would play in a little cupboard, where he could sit on a shelf and close himself in by a door, like the door of an automobile. He would take imaginary rides with imaginary stop and go lights to make the car stop and go. He then became interested in doors as such, in their knobs, keyholes and hinges and, finally, in the door checks. Door checks became an impulsion with him, which occupied him up to the time of his admission to the hospital. He was preoccupied all day with doors and door checks. He was rejected from kindergarten because he smashed the fingers of the other children in the doors. He could not play on the streets because he could not be stopped from playing with the neighbors' doors, up and down the street. He was much concerned with the shapes of doors, doorknobs, casements and hinges. The opening and closing of doors occupied him for hours. He was especially fascinated with door checks. All his questions were concerned with how doors open and close. He expressed the belief that other openings were regulated in a similar way by door checks. Thus, when told by his mother how babies are made inside the mother's uterus, he expressed the opinion that they got out by means of the door check. He would also occupy himself by the hour in drawing doors with door checks. He valued these highly and became extremely aggressive if an effort was made to take them from him or to destroy them. It was highly important in the making of these doors that they maintain certain proportions and that the plate for the keyhole and doorknob and the hinges all be square or rectangular and turned so that the long axis was vertical. If they were drawn for him so that the long axis was horizontal it disturbed him to the point of rage. Green doors and door checks were especially valuable as they represented "go," while red ones meant "stop." So far we could see, this child was much concerned with movement and the impetus for movement—for openings and the mechanisms of openings—and with the symbols for these things. When dealing with them as visual motor patterns he demanded that they conform to his concepts of such patterns, and he treasured such patterns highly. After he was in the children's ward for a month, he returned home and came frequently to the mental hygiene clinic for psychotherapy. During this time there developed new compulsions. He resented his placement in the hospital away from his mother, and was greatly preoccupied with the reasons for sending him there and with his new experiences and associates. An effort had been made to direct his good intelligence along the lines that usually interest a child of his mental age. He was taught numbers and

how to read. He was greatly preoccupied with the numbers, especially with the number 6. This is the number of the floor on which the children's ward is located. Much of the day was spent in the schoolrooms and playrooms of the roof, or eighth floor. On returning to the ward by the elevator, it was Billy's habit to watch the mechanisms of the elevator, especially a slit in the wall whereby the elevator mechanic could determine the number of the floor. The "6" was a large, open-faced figure. It was this "6" which fascinated Billy for a long time. He seemed to think that it indicated the arriving at and leaving of the ward. For months he was preoccupied with this number, as formerly he had been occupied with door checks. He made 6's with paper, crayon and clay all day long. He experimented with all kinds of 6's and noted all their characteristics. He compared other numbers with 6. Thus, he said he liked 6 best of all because it was all closed up and sad. Next to 6 he liked 2 and 5. He also liked 6 because it had an edge on one side of it, but he hated 1 because it was all edge. He did not like 7 because it was almost like 1. He said that 9 was a 6 upside down, but was not much interested in it. Owing to his increasing aggressiveness under treatment (which cannot be discussed here), he was returned to the ward about eight months after his first admission. On this occasion he became preoccupied with the dials over the elevator doors which indicate the presence of the elevator and the direction in which it is moving. These indicators had a clocklike face and nine numbers, with, as it happened, 6 at the top. At the time that he first learned his floor number he had shown some passing interest in the clock, with its numbers and moving hands. The elevator indicator, however, fascinated him completely. He thought that the indicator made the elevator come and go. He believed that the numbers on the indicator regulated the numbers on the floor, and since 6 was at the top, he concluded that all the floors in the hospital centered about this important floor. He was occupied all day long with the spatial problems of the series of floors from 1 to 9, and the circular series of numbers on the indicator, with 6 at the top. In addition, he was also preoccupied with the doors on the elevators. These were sliding doors with a little window in each of two partitions, so that when the doors were wide open, by sliding on each other, the little windows were parallel. He thus was soon able to preoccupy himself with nine sliding pairs of doors with nine indicators each, with the complete series of numbers on their face, always with 6 at the top. Now, it must be realized that he had been occupied with the philosophy of space, of sequence and therefore of time; with movements and the mechanism of movement; with doors and means of opening, and with symbols for all these things; and that by this time 6 probably represented himself. It was also a feminine number, not being penis shaped like 1. It was also a smiling and open number, not completely closed like 8. At home he often made 6's with clay or paper and crayon, and gave them to his mother as a precious gift. He could not be induced to give them to his father, with whom by this time he was on fairly friendly terms. It is not possible for us to say what are all the mechanisms that related these preoccupations with his personal experiences—with the difficulties with his anal sphincter, his hatred of his father and his own masculinity.

His reactions to the puppet shows allowed a still deeper insight into his problem. Primitive oral and anal trends and an enormous aggression came into the foreground. He was particularly preoccupied with a play called "Casper and the Devil." Day after day he would play in an impulsive manner with the puppet characters, the devil and Casper. He played the following scene: The devil appeared with a pitchfork with which he stuck Casper. Casper whimpered and

cried. The devil laughed: "I am going to take you down to hell; ha-ha-ha-ha." The devil took Casper down to hell. After that, both characters were held up again and the entire scene was reenacted. Billy was observed to repeat this scene as often as twenty times in the course of one afternoon. During the play, Billy let the devil threaten Casper by saying: "I'll cut your eyes out. I'll chop your head off. I'll cut your stomach out." On a few occasions the devil also took Billy's mother to hell. Frequently, Billy kept Casper down in hell and let the devil attack him with a pitchfork. When Billy was told that the devil was a bad character, he denied it. He said: "He is Billy's devil. I tell him to do these things."

There is not much doubt that one deals here with an extreme sadistic aggressiveness and anality. We do not attempt to exhaust the psychogenetic problem. The hate of Billy for his father was outspoken. He denied for this reason the existence of his own penis, as well as the father's penis. One might be tempted to connect the whole problem with the specific anal difficulty alone. However, in our opinion, the marital problem of the parents, rather than the problem of the local organ inferiority and of the sensations connected with it, was of major importance. It is tempting to bring Billy's primary impulsion with the stop and go signals and the door checks in relation to the partial obstruction of his anus. However, in this interpretation one needs at least a reminder that preoccupations of children in early life with the opening and closing of doors may also be present if there is no difficulty concerning the anus. Billy was fascinated with his impulsions and could hardly be induced to give up acting in this direction. As long as he performed the impulsion he was satisfied, although he sometimes remarked that he had to do so. The distress started when he was hindered by outward circumstances from following his impulses. The description makes it clear that Billy in other respects was a difficult child, full of sudden and destructive impulses. It is remarkable that these impulsions changed from period to period. All of them seemed to have a symbolic character, although they were based on real interests, such as doors, numbers and watches.

Case 4.—Lawrence was 11 at the time of his admission to the children's ward, in 1937. On the Stanford-Binet test his mental age was 15 years and 6 months and his intelligence quotient 131. In a retest in March 1938, his intelligence score was 150. The family situation was desperate. The father was a habitual criminal, who appeared at home only occasionally and was at the time serving a long term because of a fur and jewelry robbery. His mother, a lawyer, and a very intelligent person, suffered from paranoia and had been committed to a state hospital at the time that Lawrence first came for observation. The family had always lived in extreme poverty. There was 1 brother, two years younger, who was also in the observation ward of the hospital, but merely as a neglected child. He was extremely well adapted, amiable and considerate, and had an intelligence quotient of 150. He never showed any difficulties. Lawrence was brought into the hospital because he would not adapt himself either in school or in camp. He ran

away from home for hours at a time and came home exhausted. At camp he had sexual play with cats. He also tried to grab the sex parts of other boys. Once he came near girls and tried to put his hands under their skirts. His mother had never felt that there was anything wrong with him, although he had continual difficulties in school. His progress in school was poor, in spite of his brilliant gifts. When he came to the hospital he was extremely indignant and abusive. He called the hospital a jail and the other children "jailbirds" and had continual fantasies of escaping or blowing the hospital into the air. He also had fantasies that a master criminal would come and throw a bomb at the hospital, so that he and other patients could escape through a hole in the wall. He threatened suicide and, indeed, made attempts in this direction. His preoccupation with the idea of leaving the hospital exceeded by far what one would expect under ordinary circumstances. Furthermore, he repeated the same motives and the same ideas again and again. It was as though he was compelled to do so, although he did not have the feeling of being compelled.

His attitude in many other respects was similar. He was extremely preoccupied with his possessions. He wanted to get as much as he could—pencils, toys, etc.—and he was continually afraid that somebody might take them away from him. He was particularly fascinated by the idea of money. He continually asked for money and tried to hoard it. He had an exaggerated opinion of the value of the things which he owned. His attitude toward money was a compulsive one, but without the feeling of being compelled.

He had a similar relation to foodstuffs, especially candies, of which he favored specific types. He talked continually of how he could get them and devoured them with great pleasure; irrespective of how much he received, he wanted to have more. On the occasion of ward parties he made himself sick from eating. There was a continuous preoccupation with numbers. He calculated exactly not only the number of days he was in the hospital but also the number of minutes. Furthermore, he had an enormous pleasure in counting. For instance, one day he said that he had counted up to 7,999. He bounced a ball and counted the impacts until the ball was taken from him. He counted his own respirations and blew on a mouth organ with the same impulsion, to the exasperation of the ward. He drew revolving curves and lines over sheets of paper and wrote numbers on the lines, so that finally the whole crisscross of lines, and with that the sheet, was covered with numbers. Later, he extended his interests to the fantastic numbers of astronomy.

He had a passion for walking the streets. He counted the numbers on the houses and wanted to see where the streets ended. The longer the street the better he liked it. Before he came to the hospital he had walked for hours, until exhausted. (In the hospital he made maps of streets and houses, with the same end in view.) After his discharge from the hospital for the first time it was again difficult to restrain him from doing this. He used roller skates in order to extend his experiences. During his first stay in the hospital he wanted to be a motorman in a subway train.

He adjusted poorly with other children in the ward. He never tired in expressing his disgust, hate and contempt for them. He called them "criminals" and "guttersnipes." He wished that all of them would be bald. He did not form a real attachment to any one. He made occasional attempts to pinch the genitals of other boys. He denied that there was any sexuality involved in this. He stated that he merely wanted to punish them and that, in his opinion, this was the best way. At the same time, he was extremely afraid of the children and complained

continually that they were hitting and abusing him. He was cowardly in his reactions. His name was originally Howard but he had changed it to Lawrence, since the children in school recited, "Howard is a coward." He liked persons as long as they yielded to him and gave him things. To the slightest deprivation imposed on him he reacted with enormous hate.

One might say that he considered other human beings merely from the point of view of what he could obtain from them. An attempt was made to psychoanalyze him. However, his associations remained mostly on the surface. Even his dreams dealt chiefly with his immediate wishes and preoccupations. On the whole, it appeared as if there had been a strong attachment to the mother, but he had felt that he was continually exposed to deprivation. This attachment, therefore, remained superficial, intermingled with hate and fear. A strong jealousy concerning the brother was always present. Fear dominated his relations with the father. He was supposed not to know about his father's criminality; however, it appeared that he knew all about it. There were numerous dreams of fears of being kidnaped and abducted by criminals. After several months' stay in the hospital, various attempts were made to place him outside. With the help of an unusually tolerant foster mother, these attempts were successful for several months. However, he had difficulties in the public schools because he could not tolerate other children and assaulted a monitor; finally he had to come back to the school of the hospital. Further difficulties arose when he started to cover his face because he said he was ugly and people were looking at him. This hiding of the face gave the impression that it was more a whim than a real paranoid idea. However, it was so persistent that he was stopped on the street by a policeman and had to be admitted to the ward again. Psychotherapy was attempted, again without success. It was decided to use insulin treatment, after which he was more adaptable for about two weeks. He did not cover his face so persistently. However, his other behavior difficulties proved to be so severe that he had to be committed to a state hospital.

We find in this case not only overwhelming interests in numbers, streets and houses, but also actions corresponding to them. His whole psychic life was so constructed that he had either no interest or an obsessive one, an impulsion. This picture was associated with "obsessive" greediness, pertaining not only to the oral sphere but to everything in the nature of possessions. He had excessive hobbies, excessive likes and dislikes and a tendency to collect what he liked. One may suspect that the early deprivations and the wish to compensate for them may have had something to do with this picture. In spite of the unsatisfactory results of the intensive treatment, we did not feel that the diagnosis of schizophrenia should be made.

Case 5.—Amelio, aged 12, was in the children's ward during March and April 1939. He was sent there by the Department for the Study of Children with Retarded Mental Development of the Board of Education. The complaint against the child was that he was difficult to handle in the schoolroom because of his impulsive behavior, his emotional instability and his maladjustment to educational routine. He had been classified by their psychologist as a child of dull normal to borderline intelligence. There was apparently a suggestion of organic disturbance of the brain because of chorea-like motility and a doubtful family history of

venereal disease. Examination and observation revealed that the child had an intellectual endowment above average, with special disabilities and special abilities, but with deep-seated psychoneurotic problems in reaction to a psychopathic father, an unstable home situation and poor handling of his educational disability. Psychometric examinations performed shortly after admission revealed an intelligence quotient of 110, with a mental age of 13 years and 2 months on the Stanford-Binet revised form L, and a mental age of 9 years and 5 months on the Arthur point performance test. The psychologist at that time expressed the opinion that the boy was still not functioning at the maximum and noted a marked discrepancy between verbal and nonverbal performance, in that he showed an unusual capacity for handling verbal material. There were marked discrepancies here, however, as he scored at an inferior level in social judgment and insight and showed severe educational retardation in arithmetic, reading and spelling, but an unusual fund of knowledge in geography, history and astronomy. It was stated that the boy's intelligence was definitely above average and that he showed special facility in handling verbal material, but was handicapped in academic subjects and dealt poorly with performance material. He showed outstanding gifts in both graphic and plastic arts. There was, moreover, a reading disability, which tended to compensate itself by his ability in graphic art and by thorough development of verbal capacities based on information obtained by ear. His scoring on standard tests obviously suffered much by his emotional inhibitions.

Observation in the ward showed that the child was exceedingly unstable and distraught, and that he was suffering from considerable tension. It was difficult for him to apply himself to the schoolroom routine because of his inability to deal with tasks with any satisfaction to himself. There seemed to be constant impulses to draw, but even his drawings were incoherent and incomplete. During the second and third weeks of observation, when the boy was at his best, it was possible to motivate him to complete his drawing, at which time he produced some exceedingly interesting pictures—usually of wild animals attacking and killing men. These animals were mostly lions and tigers, but there were also dragons. They were usually in lively colors. Blood gushing from wounds in lively red was emphasized with particular gusto. The technical ability with which animals and persons were drawn was considerable. Of these series of pictures there was only one in which a man killed another with a sword; on this he wrote the legend: "This man is just as small as the other man, but he put on big things to look strong so he can scare and kill this other man." When he was asked what he would do if he had the power to make the world over, he wrote: "I would make the tiger and I would make the lion stronger than any men. I would make Africa and Australia stronger so they could conquer Great Britain, and would make it so that they could not die. But would let the bad people die any time, and I would be richer, better and make myself the strong man in the world."

On completion of the drawings he often applied himself well to academic objects. Otherwise, he was anxious to carry on group discussions about geography and present social events, especially in regard to Hitler and the Czechoslovakian situation. In the ward he was restless and frequently created difficulties with the other children, by whom he was not well liked.

In a psychiatric interview, the child gave evidence of being overeager; he made a good contact with the psychiatrist, showed marked capacity for verbalization and was anxious to discuss his difficulties. Briefly, his problems resolved themselves into a strong antipathy against his father and an overwhelming feeling of being defeated and thwarted in any effort to obtain satisfaction. His hatred for

his father often found concrete expression. He described his father as a slave driver of his mother, a trouble maker, who made contacts with other persons in the neighborhood only to fight with them and make trouble for the family. He stated that his father pretended to be many things that he was not, and that he claimed to have been born in many countries other than the United States. He indicated that his father considered himself too good for his own family and made no effort to work, but that he often spoke of having superior positions and thus had thrown away many chances. It was proved that the child's insight into his father's peculiarities was striking. It appeared also that the father would not allow the child any sort of satisfaction. The boy was not allowed to play on the streets, to go to moving pictures or to listen to a radio in the house. The father attempted to drive the boy to do his home work, including reading and writing, of which the child was incapable, and the boy was frequently beaten for failure. A final analysis of the child's impulsive and ticlike behavior indicated that it was an expression of the combined thwarting of his desire to express himself and of his attempt to show his hatred for his father. His dream life, his pictures, his clay work, even his dancing, all resolved themselves into some dramatic expression of an attempt to kill a man by a wild beast or other means. We treated the boy with benzedrine, hydrotherapy, intensive tutoring, artistic expression, psychotherapy and group activities, and he improved steadily for a few weeks. After that he returned to most of his former behavior, although it was partially modified. For example, his drawings were less aggressive. Undoubtedly, the boy realized that he must soon return to his home without any real solution of his problems.

This child had extremely strong aggressive impulses, directed chiefly against the father. He obviously identified himself with wild animals who kill men. He was completely preoccupied with this topic and expressed it in fantasy as well as in drawings. However, one had to keep in mind that the artistic ability which he had developed was closely connected with his reading disability; his pleasures in drawing and his capacity for it correspond closely to what has been observed in children on other occasions.[6] The special contents of these drawings and the energy which he spent on them were due not only to his reading disability but also to his specific psychologic conflicts.

COMMENT

We have described a group of cases in which preoccupations with specific ideas and fantasies, special interests in impulses and the performance of specific actions with eagerness and satisfaction dominate the picture. The ages of the children were between 4 and 12. Only 1 child, who showed the transition from this picture to an obsession neurosis, was on the threshold of puberty. We call this picture impulsion. In their clearcut form impulsions have been observed, so far, only in children. There is, however, no question but that similar phenomena can be observed also in adults whose interests are more or less bound in one direction. Impulsions have close relations to hobbies, collecting

6. Bender L., and Schilder P.: Art and the Problem Child, to be published.

and overemphasis on a particular group of actions and occupations. We shall discuss this later in more detail, after having obtained insight into the range of the phenomena described.

In Billy, there was at first an overwhelming interest in door checks and doors in general. This preoccupation expressed itself also in actions repeated over and over again. Later, the interest in specific numbers and in dials was substituted for the interest in door checks. Here, too, the interest was not merely theoretic but expressed itself also in actions. Both interests expressed themselves also in the contents of drawings. Billy had no particular tendency to resist his impulses, although he was in continual conflict with adults. He gave them the excuse that he had to do it. Generally he showed great stubbornness in following these impulsions, but it was remarkable that also outside this particular field he was obstinate and wanted to follow his own wishes only. He showed, furthermore, violent dislikes, especially for the male sex organ.

Lawrence showed the tendency to follow his impulsions, such as running and exploring the streets up to the point of physical exhaustion. Furthermore, he generally did not want to stand for any interference with his wishes. He had the feeling that they must be satisfied. He expressed violent hatred against any one who interfered with his impulsions and with his impulses. There was a particular preoccupation with counting, with numbers and with space. All this was transformed as much as possible into action. Further, he was greedy, craving money and possessions, and he attempted to collect these things—all this was with the feeling that he was entitled to all he could get. He was self righteous and self satisfied. In his relation to others he showed an enormous aggressiveness in words and wishes. Physically he was a coward and did not want to fight.

Stanley had a strong hate for his father and doubts concerning his own virility; he was preoccupied with drawing girls, and he asserted that they too had a penis and testes.

Amelio had strong aggressive tendencies against his father. He indulged in fantasies and drawings in which a beast killed a man. That he chose this expression was partially due to the fact that the drawings compensated for his reading disability.

Finally, Marvin suffered when one of his strong wishes could not be fulfilled. In order to overcome his preoccupation with the wish, he threatened himself with death and then had to overcome his fear of death by special actions. This is a case in which the impulsion was clearly the nucleus of an obsession. However, besides the obsession, the boy retained the capacity for strong desires and wishes and the necessity of having them fulfiled. There were aggressive actions in earlier childhood, followed by feelings of guilt. Since the boy felt that his wishes

should be fulfilled, he demanded and obtained from his family a bicycle, a bayonet, admission to the naval reserve and admission to and discharge from a public institution. He insisted, furthermore, that his wishes should be fulfilled promptly. His belief that he had a right to have his desires fulfilled led to the illegal acts of fishing, breaking a box together with friends and hitchhiking on trolley cars, although he realized the dangers involved. When he fell off a trolley car and broke his arm he was preoccupied in a hypochondriacal way with the fracture, especially after it was cured.

These observations show the wealth of symptoms in these cases. We repeat them: (1) continuous looking at and handling of a specific object; (2) drawing of this object; (3) preoccupation with this object in fantasies or in thoughts; (4) excessive walking; (5) counting and preoccupation with numbers and space; (6) strong desires, wishes and demands for immediate satisfaction; (7) resistance and hate directed against any interference; (8) greed concerning food and money; (9) collecting and hoarding; (10) hypochondriacal preoccupation; (11) stubbornness, and (12) social actions which satisfy the strong desires.

This picture has not found specific attention, as far as our knowledge goes.[7] We might indicate that it has a close relation to compulsions and obsessions. However, in the case of compulsions and obsessions the subject protests against his impulses and thoughts. It is true that our patients also from time to time were bothered by their impulses. However, their inner protest was not as inherent a part of the picture as is the case with compulsions and obsessions. It is true that obsessions and compulsions are at times accepted or not protested by the patients. However, this is the exception and not the rule. On the whole, one might characterize the difference by saying that in the case of compulsions and obsessions the patient protests with his ego and superego against his impulses, whereas in the case of impulsion, this protest is weak or nonexistent. One may understand in this way that impulsions are more characteristic of childhood and compulsions and obsessions of adolescence and adult life. This statement should not be understood in a schematic way. Features of obsession neurosis have been repeatedly observed in early childhood and are also to be found in our material. Fenichel cited several cases of early obsession neurosis. However, the question arises whether at least some of the so-called obsessions and compulsions in children are not impulsions in the sense described here.

7. There exists a children's story, entitled "Susanna B. and William C." by Rachel Field, in which impulsions are clearly described. Susanna has an overwhelming interest in shoes. She is magically punished by finding shoes which force her to dance forever. William is too curious about locks and keys. He is finally magically forced to wear a mailbag through life. Such a story, with its complete lack of understanding and sympathy, could only be deleterious to children.

Klein [8] expressed the opinion that obsession neurosis plays an important part in the neuroses of children. Obsessional neurotic trends serve, in her opinion, the attempt to overcome the psychotic anxiety of the earliest levels of development. However, she stated that this early obsession neurosis is different from the later form. Indeed, she mentioned ceremonies, exaggerated orderliness and cleanliness as symptoms of the earlier neurosis. These, too, are symptoms which are generally accepted or are acceptable to the subject. The adult with an obsession neurosis, on the other hand, shows character changes which correspond closely to the impulsions as we have described them in children. They are tolerated by the ego, or are even considered as a valuable part of the ego. Orderliness, cleanliness, parsimoniousness, collecting and hobbies in general belong in this category. However, if one compares the obsession neurosis, which may be present even without obsessions or compulsions, with impulsions one sees immediately that whereas the impulsions are hardly socially acceptable the obsession neurosis character trends are acknowledged by ego and society. In other words, whereas in the impulsions the ego is not concerned or is not considered as important, in the obsession neurosis the impulsions have been integrated, more or less perfectly, into the ego system. This is again understandable from the point of view of a difference between childhood and adulthood in respect to the organization of the ego.

In spite of this, it would be wrong to believe that the impulsions as described here are the direct expression of primitive wishes. They have a complicated individual history and can be characterized as symbolic, as in Billy's case, in which the opening of the door pointed to his anal difficulties. The running, exploring and counting in Lawrence's case have certainly not only a manifest content but an unconscious meaning, and the same is true of the drawing of Stanley and Amelio. Complicated processes of interpretation are also necessary to understand the impulsions displayed by Marvin.

It is worth while in this connection to point to the enormous aggressiveness which is represented in the impulsions and their allied phenomena. This is either direct aggression or curiosity, or aggression hidden in counting. In the majority of cases the impulsion often serves aggression in connection with the father problem. Only Stanley's problems were concerned with castration and femininity alone. It is perhaps worth while to mention that we have so far observed impulsions only in boys.

The aggression in these cases is by no means merely sadistic. In these impulsions there is a great deal of curiosity, the wish to learn

8. Klein, M.: Psychoanalyis of Children, translated by A. Strachey, New York, W. W. Norton & Company, Inc., 1932.

and handle and the wish to experiment. This leads to the general problem of overwhelming interests in early childhood. We have observed in very young children that they have a close relation to the pillow. This may already be present in the second or third month. These children clutch their pillow primarily in order to be more secure in their equilibrium. They want to have something, to have hold on it. Later, they retain the need for the pillow. It is gratuitous to say that the pillow serves the overcoming of anxiety and that this defense is retained. The anxiety has, in some way, to do with the maintenance of the equilibrium. When children start to crawl, at the age of 8 or 9 months, they become deeply interested in doors. They play with doors and handle them well. This interest may last for several months, only to be replaced by another, such as wall plugs or light connections. These interests we have observed in children from 12 months to 2 years of age, when they shift to flags, boats, books and other objects. One might say that these overwhelming interests lead to a better acquaintance with the objects. They belong, therefore, to the ego instinct. They may retain their importance when libidinous motives lead in a similar direction. We are inclined to believe that this was so in our cases. This interest is as well a transformed infantile curiosity and experimentation as a strong desire for satisfaction in the family circle.

In all our cases, transformations and symbolizations, although they took place, did not go as far as in the character trends which appear in the adult. Such impulsive character trends can be found not only in the patient with an obsession neurosis but also in the criminal who displays impulsions. One may suspect that deep genuine interests which lead to useful preoccupation in science and work have a genesis comparable with that of impulsions.

It might be worth while to complement these observations from various angles. One might try to classify the possible impulses and impulsions of childhood. There are the impulses of sex that emerge more or less directly in premature sex activities, which may be directed toward other children or may be autoerotic. One might, furthermore, find impulses concerned with motor activities in the narrower sense. Here belong rocking, hitting the head against the wall and manneristic and automatic movements. There might also be mentioned too much interest in motor play and, finally, running away. As a third group, one might think of destruction and tearing, irrespective of the object. The fundamental change in the system of motor impulses occurring in and after encephalitis often induces pictures somewhat similar to impulsions. They differ in that in the majority of cases of encephalitis the impulses are less organized than in the impulsions. However, there are cases of postencephalitis occurring in adults in which the impulses

are organized as impulsions, and one may find also pictures in which impulsions, compulsions and obsessions are present at the same time.

Most of these impulses and impulsions are not so much persistences of more primitive levels of expression as a return to these levels when expression on a higher level is frustrated. One might, furthermore, express the opinion that even these primitive actions and interests are modified by the total situation and have, therefore, in addition to their direct meaning, a symbolic one. It is significant that most of the children in this series made poor adjustments at school and had various educational difficulties in spite of good intelligence.

This becomes more obvious if one considers the forms of impulsive eating (particular emphasis on specific foodstuffs or eating rituals) and impulsive fighting and hitting other children. Habitual stealing and fire setting (Yarnell [9]) have a still more symbolic structure, and many of the motor habits and ticlike mannerisms which the child cherishes are in no way a simple expression of primary impulses. One might, furthermore, draw attention to all so-called criminal acts in children and adolescents. One will understand that in many such patients the constitutional motor and instinctual endowment plays an outstanding part. Some of the drives leading to impulses may be decidedly organic, although the group described here did not show such characteristics.

We have mentioned before that the so-called obsession neurosis of childhood might not be really such. Yaskin [10] wrote, for instance, that he found neurotic trends existing from childhood in compulsive-obsessive reactions . . . "but [they] were thoroughly integrated in the personality make-up and did not produce disabling symptoms until somewhat later in life." Our own experiences in analyses of adults suffering from obsession neuroses did not disclose such trends in the narrower sense before prepuberty. However, there were many indications that impulsions were present. Moreover, we have observed children of about 11 or 12 years in whom the first symptoms of obsession neurosis had appeared at the age of 7. We are therefore inclined to believe that impulsions against which the ego and superego do not take a particularly strong stand are more characteristic of earlier childhood. They occur up to the age of 10 or 12 years. Later, toward puberty, obsessions and compulsions make their appearance. In the impulsions, some transformations have taken place under the influence of the ego and superego system. At about the age of 10, sometimes earlier, sometimes later, the ego and superego take a definite stand, and the impulsions either

9. Yarnell, H.: Firesetting in Children, Am. J. Orthopsychiat. **10**:272 (April) 1940.

10. Yaskin, J. C.: The Psychoneuroses and Neuroses, Am. J. Psychiat. **93**:107-125 (July) 1936.

become compulsions or are integrated into the total character as so-called obsession neurosis character trends. These character trends, as well as the impulsions, therefore, express primitive impulses and are tolerated by the ego-superego system, but, in accordance with the greater demands of the system in later years, the primitive desires have had to undergo more thorough transformation in order to be accepted as character trends.

CONCLUSION

A group of cases is described in which specific interests, ideas and actions dominate the clinical picture and make social adaptation impossible. We have called these pictures impulsions. We have found them in boys between the ages of 4 and 12.

Impulsions and compulsions may be observed together at the beginning of puberty.

The symptomatology comprises: continuous looking at and handling of a specific object; drawing of the object; preoccupation with the object in fantasies or in thoughts; excessive walking; counting and preoccupation with numbers and space. The subjects insist on immediate fulfilment and satisfaction of their wishes. They cannot stand any interference with the fulfilment of their desires. There may be greed concerning food and money or a tendency to collect and hoard. The patients are stubborn, show hypochondriacal preoccupations and may use asocial means to satisfy their strong desires.

The impulsions take their origin from early infantile situations and desires, and can be compared with the preoccupations of children before they are 2 years of age. They are never direct expressions of sexual motor and aggressive drives, but are always related to the family situation and are, therefore, in many respects the result of transformations. However, owing to the inefficiency of the ego-superego system at this age, the transformation is not as far reaching as it is in patients with obsessional character trends, which otherwise have a similar genesis.

It seems that true obsessions and compulsions are rare before the age of 10 years. In the early history of patients with adult obsession neurosis indications of impulsions can be found.

Impulsions give to the objective observer the impression of compulsions and obsessions, but are differently experienced by the child.

MOTOR PHENOMENA DURING NITROGEN INHALATION

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Himwich, Alexander and Lipetz,[1] reasoning that the effects of insulin and metrazol treatments in cases of schizophrenia are due to a common factor, namely, the production of cerebral anoxia, introduced the nitrogen inhalation therapy. They have already described the manifestations occurring during this type of treatment. We are interested in more detailed observations of the neurologic phenomena evidenced during this procedure, especially the motor sequence.

MATERIAL AND METHOD

The procedure of Alexander and Himwich [2] was initiated at Bellevue Hospital by Bowman, Green and Adriani, who will report on the clinical findings. The technic, except for minor variations, is essentially the same. The apparatus consists of an anesthesia mask, which is connected in series to a canister of soda lime and a breathing bag. The oxygen is supplied by means of an ordinary gas machine, and the nitrogen is delivered from a large tank of commercial gas. The carbon dioxide is removed by the soda lime, thus reducing the discomfort of the patient. The apparatus is first filled with pure oxygen, and when the patient has had a few breaths, nitrogen is run into the mask, gradually displacing the oxygen. In the meantime frequent readings of the blood pressure and pulse rate are taken.

The treatment is generally continued until severe motor phenomena are present and the patient is deeply unconscious. In most of the cases the procedure did not take more than two minutes, which is a somewhat shorter period than that required in Himwich's method. However, on occasion the treatment was continued up to four or five minutes and in some cases was extended to ten or fifteen minutes. This prolongation was made possible only by reducing the oxygen content of the inhalation mixture more slowly or by occasionally adding small amounts of oxygen.

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From the Division of Psychiatry, Bellevue Hospital, and the Department of Psychiatry, New York University Medical College.

1. Himwich, H. E.; Alexander, F. A. D., and Lipetz, B.: Effect of Acute Anoxia Produced by Breathing Nitrogen on the Course of Schizophrenia, Proc. Soc. Exper. Biol. & Med. **39**:367 (Nov.) 1938.

2. Alexander, F. A. D., and Himwich, H. E.: Nitrogen Inhalation Therapy for Schizophrenia, Am. J. Psychiat. **96**:643 (Nov.) 1939.

RESULTS

The following description is valid for the short and the somewhat longer treatments. However, it will be necessary to add a comment on treatments which were prolonged to ten or fifteen minutes, because here the phenomena were qualitatively and quantitatively different.

Short Treatment.—The motor sequence exhibited by patients undergoing the relatively short nitrogen inhalation therapy may be divided into four more or less distinct phases, which tend to overlap.

Stage of Restless Movements: This stage starts shortly after the inhalation of nitrogen is begun. Usually, the first thing to occur is a restless moving of the lower extremities, consisting chiefly of crossing and recrossing of the legs. This is sometimes associated with slight flexion at the knees. Often the patient will rub his feet and legs together. Inward and outward rotation of the legs is also common, together with plantar flexion and extension of the toes and feet. Often one has the impression that the patient tries to stop these movements and therefore presses the legs against each other in an attempt to fixate them. These movements occur soon after the diminution of the oxygen content of the inhalation mixture is begun. It is interesting to note that some patients who have had several treatments previously show these restless movements as conditioned reflexes the moment they are wheeled into the room, before nitrogen inhalation is started. At the time when the restless movements appear, ankle clonus may be present. This becomes more apparent as the treatment progresses. Patellar clonus is rare. The clonus is not well sustained and has the characteristics of clonus seen in cases of paralysis agitans, with a tremor-like quality, as compared with that of pyramidal tract origin. The patients are still able to count at this point. Pupillary changes occur at about the same time. The pupils become large and react sluggishly to light. With the progression of the treatment the pupillary reaction becomes still worse. The clonus, the restless movements and the pupillary changes appear approximately at the same time, although one may precede the others.

It has been noted that in this and in the two following stages any attempt to elicit the abdominal and plantar reflexes tends to increase the motor phenomena. It may be mentioned that during the entire course of the treatment the abdominal reflexes are persistently present and Babinski, Oppenheim or Rossolimo signs are never obtainable.

Myoclonic Phase: This follows the first stage. Myoclonic twitches occur around the mouth, in the flexors of the arms, in the extensors of the knees and in the flexors of the foot. These twitchings are usually irregular and are often associated with a myoclonic dorsiflexion of the big toe.

Rhythmic Phase: The myoclonic twitches increase and approach a rhythm consisting of symmetric extension of the knees and feet. This may become alternating, so that it appears as if the patient were stamping his feet. Occasionally, the myoclonic twitches may resemble coarse tremors. Toward the end of this stage the pupils become fixed to light in middilatation. At this point many patients close their eyes violently, and there is a great deal of resistance when an attempt is made forcibly to separate the eyelids. Conjugate deviation of the eyes may occur in either a horizontal or a vertical plane, with slow rolling movements in any direction.

Tonic Phase: The myoclonic twitches become more tonic in character. They become prolonged and finally melt into each other in tonic postures. In the

upper extremities one usually sees, at first, flexion of the elbows, with extension of the fingers, and flexion of the hands. A grasp reflex may be present; however, it is transient and of low intensity and is not common. In many cases the flexion is combined with abduction and raising of the arms. Occasionally the flexion is followed by an extension of the arms, with pronation and abduction. The shoulders are pulled downward. The extension sometimes precedes the flexion.

In the lower extremities the common posture is one of extension and abduction. Later there may be some flexion in the knees and hips, with dorsiflexion of the feet. This may be more marked on one side than on the other. One or both of the lower extremities may be raised in the air, extended at the knee and flexed at the hip. At the height of the extension, arching of the back occurs, with retraction of the head, producing a complete picture of decerebrate rigidity, with extension and pronation of the extremities. At this point the Magnus-de Kleyn reflex is obtainable. Turning the head usually produces chin-arm extension and occiput-arm flexion. The lower extremities as a rule do not follow suit. Sometimes a paradoxic response is obtained during this maneuver, with chin-arm flexion and occiput-arm extension. Now the pupils are greatly dilated and do not react to light, and the eyes remain fixed in one position.

Recovery: Usually at this point pure oxygen is given. The tensions continue, and sometimes one obtains the impression that the extensor rigidity of the lower extremities changes to the flexor type. However, a careful check-up shows that when extensor rigidity has persisted under oxygen deprivation it will change to flexor rigidity before oxygen is administered. It seems that the change in the phases may be facilitated by the administration of oxygen. The situation in the upper extremities appears to be similar.

A few seconds after the oxygen is given the rigidity changes to myoclonic twitches, and the myoclonic twitches change to rhythmic movements and finally to restless movements again. In other words, there is now a transition from phase 4 to phase 1, in reverse order. The ankle clonus appears immediately after the severe rigidity, which has caused it to disappear, is relaxed. It is more easily obtained in the recovery stage than in the first four stages. In the same way, the pupils and the ocular movements return to normal in the reverse order. In the majority of cases the pupils return to normal quickly. Occasionally the pupillary reactions may become sluggish when pressure is applied to the abdomen.

It should be emphasized that during the entire procedure the reflexes are slightly increased and that at no time is a Hoffmann, Babinski, Rossolimo, Oppenheim or Chaddock sign elicited. The abdominal reflexes are obtainable as long as the tensions in the abdominal muscles do not prevent their appearance.

The patients retain the capacity for counting up to the beginning of the rigid state. There are never any aphasic difficulties. They are able to pronounce clearly and distinctly. This is likewise true after awakening, at which time they have no difficulty with the gestalt and Goodenough tests. The unconsciousness seems to last a comparatively short time. The patients are emotionally unchanged after the treatment is over. A few become incontinent of urine during the tonic phase. Most of the patients vigorously deny that they have been unconscious at all. Some of them state that they had a choking sensation under the mask, with difficulty in breathing, while others deny this.

The short treatments and the treatments of medium length are similar, except that in the latter the sequence of events is spread over a somewhat longer time. The individual differences occurring in the patients are not marked. However, each person has his specific pattern, which is repeated with every treatment.

In 1 case neurologic signs did not develop and the patient passed into a flaccid state, so that treatment had to be interrupted before tonic phenomena appeared. However, in the treatments which followed a slight variation in technic was sufficient to evoke a typical tonic response.

Prolonged Treatment.—The neurologic picture during the long treatment differs considerably from that just described. The restless movements begin at about the third minute of treatment and last for about three minutes. The tensions and the myoclonic twitchings are less dramatic, as if the same amount of muscular tension were spread over a longer period. There is a tendency on the part of the patient to become completely flaccid and to lose the abdominal reflexes. The same is true for the patellar and achilles tendon reflexes, although the latter are generally more resistant and persist for a longer time. The plantar reflexes may disappear completely but are never replaced by the Babinski toe responses. A Hoffmann sign is occasionally observed, but this is variable.

In this procedure the tonic phase is not observed at the termination of the treatment. Instead, there is a tendency toward flaccidity at this point, so that decerebrate postures do not occur. When more oxygen is given, rigidity may occur and the reflexes return.

In 1 case it was observed that the hands became completely anemic and cataleptic. This condition, however, was restricted to the hands and seemingly was the result of local anemia. At times the hands show tetanic postures.

After pure oxygen is given, the twitches and the restless movements recur in the reverse order. The unconsciousness in patients undergoing this treatment is deep. They remain confused afterward and show a changing attitude toward the environment. The pupillary disturbances persist for some time. In 1 instance aphasia was observed immediately after the patient awakened. At the termination of the treatment psychologic changes were noted. One patient showed a negative transference to the physician, which was characterized by aggressive and resistive behavior, and another patient began to call for her mother. Because of the dangerous systemic reactions occurring during the long treatment, the number of patients was limited to 2. Therefore, the results have no statistical value and are preliminary.

COMMENT

Observations of this kind are interesting, since knowledge of the results of cerebral anoxia is still limited. Studies have been made on human subjects in whom the carotid arteries were ligated. Fetterman and Pritchard [3] and Wortis [4] have reported such cases, in which hemiplegia, aphasia, convulsions and deterioration of personality were shown clinically. However, such a procedure obviously produces much more than cerebral anoxia, because there is interference with the circulation and with the removal of waste products. Moreover, there are other factors to be considered, such as vascular anomalies, previous pathologic changes and reflex activities.

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3. Fetterman, J. L., and Pritchard, W. H.: Cerebral Complications Following Ligation of the Carotid Artery, J. A. M. A. **112**:1317 (April 8) 1939.

4. Wortis, H.: A Case of Cerebral Degeneration with Encephalographic Study Eight Years After Common Carotid Ligation, Am. J. M. Sc. **192**:517 (Oct.) 1936.

Careful studies were made by Courville [5] on narcosis produced by nitrogen monoxide. Again, however, certain difficulties are encountered because of the narcotic effect of the anesthetic. His findings are remarkable for the amount of severe cortical degeneration. This corresponds to his observation of convulsive seizures and signs of implication of the pyramidal tracts, such as the Babinski reflex, in most of the cases. Aphasic manifestations were present in some of the cases.

The method used in animal experimentation consisted chiefly of eliminating the circulation to the brain. Grant, Weinberger and Gibbon [6] showed that cats subjected to periods of circulatory arrest up to five minutes and ten seconds recovered entirely within twenty-four hours and remained normal throughout the survival period. A group of cats in which circulation was arrested for from three minutes and twenty-five seconds to five minutes and forty-five seconds showed motor weakness for from two to seven days, which then disappeared. However, the behavior of the cats became permanently altered. They showed marked apathy and indifference. Animals subjected to circulatory arrest for from six minutes and seven seconds to seven minutes and five seconds remained in coma for a number of hours and showed tonic spasms, clonic convulsions, bouts of intense hyperactivity and profound evidence of cerebral cortical damage. Cats with circulatory arrest for longer periods remained in coma for many hours and had tonic and clonic fits, decerebrate attitudes, paralyses, spasticities and gross tremors.

Pathologically, the animals subjected to the longest periods of circulatory arrest compatible with life showed marked disintegration and necrosis of the cortex, with involvement of the basal ganglia, thalamus, hypothalamus and geniculate nuclei. The pons, medulla and spinal cord appeared normal except for degeneration of the pyramidal tracts. With the lesser degrees of anoxemia the basal ganglia and the cortex were involved, while finally the brains of cats that showed permanently altered behavior during life presented diffuse areas of nerve cell degeneration, seen chiefly in the cortex, the other nerve structures appearing to be intact.

The oxygen need of the central nervous system is obviously not the same in all parts. Dixon and Meyer found that there is a higher rate of oxygen consumption for the cerebellar cortex than for the cerebrum,

5. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936; Untoward Effects of Nitrous Oxide Anesthesia, with Particular Reference to Residual Neurologic and Psychiatric Manifestations, Mountain View, Calif., Pacific Press, 1939.

6. Grant, F. C.; Weinberger, L. M., and Gibbon, J. H., Jr.: Anoxemia of the Central Nervous System Produced by Temporary Complete Arrest of Circulation, Tr. Am. Neurol. A. **65**:66, 1939.

as well as a high value for the cornu ammonis. Gerard,[7] experimenting with guinea pigs, found that the respiratory rate of the medulla is hardly one-third as high as that of the cerebrum. At the lower end of the scale is the cervical sympathetic ganglion, which can resist anoxemia for almost one hour, while the neurons in the central nervous system become electrically quiescent a few seconds after the nutrient artery is clamped. The survival time, that is, the duration of anoxia after which revival with oxygen is possible (measure of reversibility), was found to be as follows: motor cortex, fifteen seconds; corona radiata, twenty seconds; geniculate body, fifteen to thirty seconds; cerebellum, ten seconds, and medulla, fifty seconds. Even if one takes these statements for granted, they have not been proved to be correct for man. Furthermore, it is not known whether the rate of oxygen consumption determines the onset of the clinical symptoms.

Our observations show that the motor phenomena occurring during nitrogen inhalation therapy do not present any of the characteristic signs of implication of the pyramidal tracts. The persistent absence of the Babinski sign is remarkable in this respect. We must stress that the myoclonic twitches and the rhythmic movements present are often associated with more or less isolated dorsiflexion of the big toe. However, this is a phenomenon with an extrapyramidal basis and has been already observed by the Vogts as such. The abdominal reflexes remain unaltered throughout the treatment. Furthermore, aphasic signs and convulsive seizures were not observed during the short treatment. The absence of these criteria indicates that definite damage to the motor sphere was not present. This does not, of course, exclude the possibility of involvement of the cortical region. It may be possible to postulate the presence of a lesion in the premotor area in connection with the restless, rhythmic and myoclonic movements. However, association of these phenomena with striopallidal or midbrain structures seems more probable. One may still assume that cortical damage liberates these activities, but such an interpretation seems to be much more arbitrary than the statement that the phenomena observed in these cases are related to the functions of subcortical mechanisms.

After the appearance of tremors and myoclonic movements, the treatment terminates in a picture of decerebrate rigidity. The elimination of the cortex alone is not sufficient to provoke such a picture, which generally appears only after there is an interruption in the brain stem below the level of the red nucleus. The sequence of the motor events and the symptomatology speak strongly against the idea that the cortex is attacked first. The restless movements, the tremors and the myoclonic movements certainly have not the character of phenomena occurring after cortical lesions.

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7. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938.

This is, at any rate, what immediate observation shows. On comparing these observations with those of Courville in cases of narcosis induced by nitrogen monoxide, one might say that Courville found predominantly cortical lesions. Still, the Babinski sign, convulsions, aphasia and changes in the abdominal reflexes were observed. Phenomena of the same type are present in patients given insulin and metrazol, during insulin coma and after awakening from the metrazol shock.[8] One might say that, according to Himwich and his co-workers, cerebral anoxia is of fundamental importance in such cases. Insulin hypoglycemia produces cerebral anoxia by limiting the supply of dextrose to the brain. It has been shown that the brain metabolizes only dextrose and that in the absence of this the oxygen uptake is diminished.[9] The metrazol shock treatment produces cerebral anoxemia by interfering with respiration during the convulsion.[10]

However, if anoxia is the basis of these reactions, it must differ from the anoxia in our cases. Metrazol certainly has other effects, as is true of insulin. There are probably quantitative factors as well as factors of distribution of the anoxia. The hemoglobin saturation of the blood during metrazol convulsions may be as low as 40 per cent. The figure is still lower during nitrogen inhalation.[1] This consideration, that the distribution of the anoxia in time may change the picture considerably, gains greater probability when one considers that the long nitrogen treatment certainly has different qualitative effects. Not only is the motility picture different, but the changes in consciousness during and after treatment are much more outspoken. However, it is not probable that the picture observed during insulin and metrazol treatments is due merely to anoxia, even when one considers the difference in sequence and distribution of oxygen deprivation.

Fraser and Reitmann [11] have come to the same conclusion regarding metrazol shock. In a study of the effects of short periods of severe anoxia induced by nitrogen inhalation, they commented on the lack of convulsive phenomena and the differences in the neurologic manifestations as compared with those occurring during metrazol treatment. They concluded that anoxia is not to be regarded as the most important mechanism of the action of metrazol.

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8. Himwich, H. E.; Frostig, J. P.; Fazekas, J. F., and Hadidian, Z.: The Mechanism of the Symptoms of Insulin Hypoglycemia, Am. J. Psychiat. **96**:371 (Sept.) 1939.

9. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Metabolism of the Brain During Insulin and Metrazol Treatments of Schizophrenia, J. A. M. A. **112**:1572 (April 22) 1939.

10. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

11. Fraser, R., and Reitmann, F.: A Clinical Study of the Effects of Short Periods of Severe Anoxia, with Special Reference to the Mechanism of Action of Cardiazol "Shock," J. Neurol. & Psychiat. **2**:125 (April) 1939.

There is loss of consciousness at the height of the nitrogen treatments of short and of medium duration. On awakening the patients are amnesic for this loss of consciousness. They awaken immediately after the treatment is terminated and do not show any deep confusion. Disturbances in the gestalt function and the Goodenough drawing, which appear after treatments with insulin [12] and metrazol,[13] do not occur here. The short loss of consciousness comes on much later than the motor phenomena. One might postulate that the loss of consciousness is due to cortical involvement, but it seems more probable that subcortical factors play at least a partial role.

The psychologic changes occurring after the short nitrogen treatment are practically nil as far as transference is concerned, while they are outspoken after insulin and metrazol [14] therapy and also after the long nitrogen treatment. At present it is impossible to understand the neurologic basis for these differences. We, at any rate, are inclined to believe that subcortical, subthalamic, midbrain and even medullary factors are responsible for the changes in consciousness. However, this point may be argued.

There exists an extensive literature on the effects of low oxygen tension on psychologic functions.[15] Lately Kagan and Barach, at the Bellevue Hospital, have studied the effects of breathing an atmosphere containing 13 per cent oxygen. The patients showed emotional disturbances and drowsiness. At present one does not know enough about the neural basis of higher psychologic processes to justify any conclusion, but there are correlations between subcortical lesions (subthalamic and in the walls of the third ventricle) and the sleep function. The deeper degrees of unconsciousness may even be related to structures in the medulla. The absence of the tendon reflexes during the prolonged nitrogen treatment is probably of spinal origin.

It is our contention that short and acute oxygen deprivation affects, primarily, subcortical motor functions and spreads from subcortical to cortical structures. This may partly explain the changes in consciousness. We should be inclined to say that the absence of abdominal reflexes, the appearance of the Hoffmann sign and aphasic manifestations in the

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12. Orenstein, L. L., and Schilder, P.: Psychological Considerations of Insulin Shock Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **88**:397 (Oct.) 1938.

13. Fingert, H. H.; Kagan, J. R., and Schilder, P.: The Goodenough Test in Insulin and Metrazol Treatment of Schizophrenia, J. Gen. Psychol. **21**:349 (Oct.) 1939.

14. Schilder, P.: Notes on the Psychology of Metrazol Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:133 (Feb.) 1939.

15. McFarland, R. A.: The Effects of Oxygen Deprivation (High Altitude) on the Human Organism, Report 13, United States Department of Commerce, Bureau of Air Commerce, 1938. Thompson, J. W., and Corwin, W.: Experimental Anoxemia, Arch. Neurol. & Psychiat. **40**:1233 (Dec.) 1938.

long treatment are due to spread to the cortical structures, and should at the same time assume that the spread takes place to the medulla and the spinal cord.

Pupillary abnormalities often precede any other phenomena during nitrogen inhalation therapy. Bender [16] has produced pupillary dilatation by stimulation of the frontal cortex of monkeys. However, it seems more probable to us that the pupillary changes present in our cases were due to the effect of anoxia on the brain stem. Since we intend to discuss the pupillary changes in detail in another communication, we shall not elaborate further on this point.

It is interesting that the restless movements are semivoluntary and can be provoked as conditioned reflexes. A subcortical neural background is certain to be present here. One deals probably with complicated interactions between an organic nucleus of subcortical character and the reactions of the total personality. This phenomenon is somewhat characteristic for a large group of motor reactions which have not yet been studied sufficiently. They correspond to a phase sometimes observed during insulin treatments, in which wild mannerisms of a similar type may be found.

SUMMARY

The neurologic phenomena occurring during nitrogen inhalation have been described. During relatively short periods of cerebral anoxia produced by this technic, the motor sequence may be divided into four phases, namely, the stage of restless movements, the myoclonic phase, the rhythmic phase and the tonic phase. With the administration of oxygen, recovery takes place, and there is a transition from the fourth to the first phase, in the reverse order. At the height of the treatment there is loss of consciousness, for which there is amnesia on awakening. No sequelae follow this procedure.

When the nitrogen inhalation is prolonged up to from ten to fifteen minutes the manifestations are different. Then there is a tendency toward flaccidity, with elimination of the tonic stage. The state of unconsciousness is deeper and the patients remain confused and show psychologic changes. Signs of involvement of the pyramidal tracts (Hoffmann sign and absence of the abdominal reflexes) and aphasic difficulties occur only during the course of the long treatment.

These findings are different from those in other types of cerebral anoxia, such as that occurring during nitrogen monoxide anesthesia, hypoglycemia and metrazol treatment of schizophrenia. We wish to stress the absence of any reliable signs of cortical involvement during short periods of nitrogen inhalation, such as convulsions, aphasia and evidence of implication of the pyramidal tracts. The probable subcortical character of the manifestations has been discussed.

16. Bender, M.: Unpublished observations.

SENSORY AND MOTOR ROOTS OF THE GLOSSOPHARYNGEAL NERVE AND THE VAGUS-SPINAL ACCESSORY COMPLEX

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Previous study of the histologic structure of nerve roots [1] has provided criteria for the differentiation of sensory and motor roots. On the basis of these criteria it was possible to demonstrate that the glossopharyngeal nerve and the vagus-spinal accessory complex contain certain roots which conform in structure to motor roots and others to sensory roots. It was my purpose in this study to follow the nerve fibers of these roots to their respective nuclei in the medulla oblongata and thus to test these conclusions.

MATERIAL

The material for this study consisted of the brain stems of a 7 month premature human fetus, a full term newborn infant and a human adult, all of which were stained for myelin sheaths by the Weigert-Pal technic. In addition, the brain stem of a human adult was sectioned and stained with thionine for nerve cells after fixation in alcohol, and another was impregnated for axis-cylinders by a modification [2] of the Gros-Bielschowsky technic. All material was embedded in pyroxylin and studied in serial sections from the level of the trigeminal nerve well into the caudal part of the fourth ventricle, past the middle of the inferior olivary nuclei.

RESULTS

The glossopharyngeal nerve contains a large bundle of nerve fibers which, in preparations impregnated for axis-cylinders and in Weigert-Pal stains, may be seen clearly to terminate in the nucleus of the tractus solitarius. Thionine preparations show the characteristic small nerve cells, with scant and finely dispersed Nissl bodies, in the nucleus of the tractus solitarius. In addition to the main bundle of fibers, a

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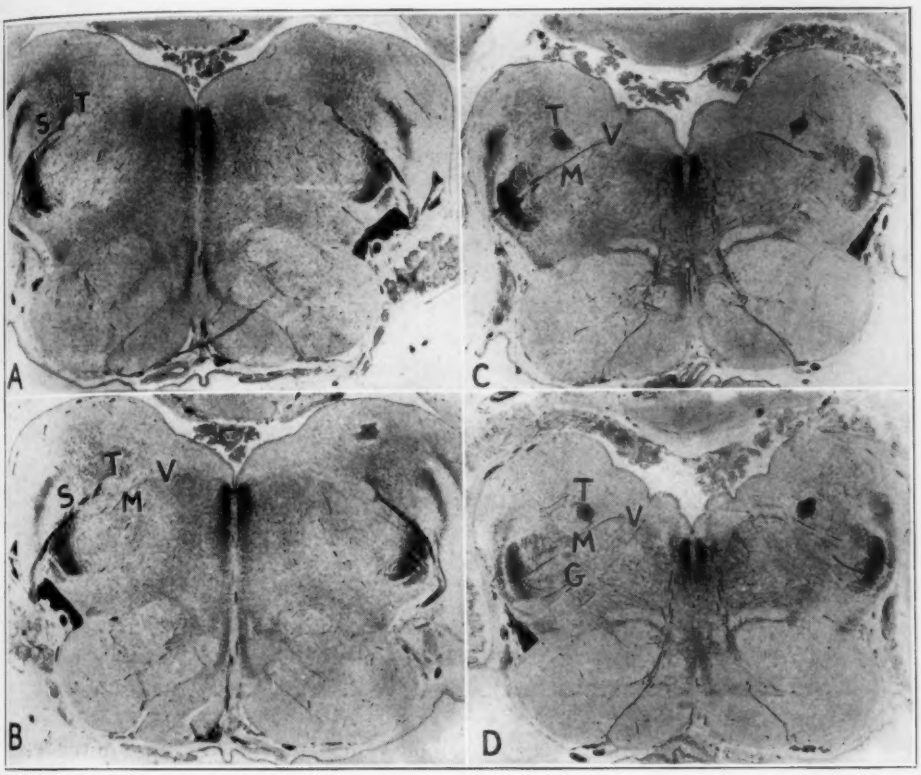
Read before the American Association of Neuropathologists, Rye, N. Y., June 6, 1940.

1. Tarlov, I. M.: Structure of the Nerve Root: II. Differentiation of Sensory from Motor Roots; Observations on Identification of Function in Roots of Mixed Cranial Nerves, Arch. Neurol. & Psychiat. **37**:1338 (June) 1937.

2. This technic, which requires special fixation, is now in the stage of experimentation in this laboratory.

very small group of nerve fibers may be seen lying medial and ventral to the main trunk, entering the region of the dorsal nucleus of the vagus nerve and the nucleus ambiguus. The large multipolar cells, with large discrete Nissl bodies, of the nucleus ambiguus may be readily



Photomicrographs taken from serial sections of the brain stem of a 7 month human fetus, showing the gradual transition from the cephalic (*A* and *B*), predominantly sensory roots to the caudal (*C* and *D*), predominantly motor roots of the vagus-spinal accessory complex. In *A* almost all of the fibers (*S*) enter the nucleus of the tractus solitarius (*T*), a few fibers pursuing a medial course and passing in the direction of the dorsal nucleus of the vagus (*V*, in *B*) and the nucleus ambiguus. In *B* the medial fibers (*M*) are more prominent, although the fibers of the nucleus of the tractus solitarius predominate. In *C* and *D* the fibers of the nerve roots arise from the region of the dorsal nucleus of the vagus and the nucleus ambiguus (*G*), practically no fibers entering the nucleus of the tractus solitarius. The glossopharyngeal nerve presents the same appearance as that in *A* and *B*. Weigert-Pal stain; × 4.5.

Serial sections of the brain stems of a full term human fetus and a human adult stained by the Weigert-Pal technic and serial sections of a human adult impregnated with a silver nitrate technic for nerve fibers (method referred to in text) demonstrate the same predominantly sensory character of the main cephalic roots and the predominantly motor character of the caudal roots.

differentiated from the more dorsally and medially situated medium-sized cells of the dorsal nucleus of the vagus nerve, with their less well defined Nissl bodies.

The uppermost roots and nerve fibers of the vagus present the same arrangement as those of the glossopharyngeal nerve (figure): A large dorsolateral bundle terminates in the nucleus of the tractus solitarius, and a few ventromedial fibers arise from the region of the dorsal nucleus of the vagus, possibly also from the nucleus ambiguus. The fibers from the main trunk pass through the nucleus and descending tract of the trigeminal nerve, and it is possible that a few fibers terminate there. As one traces caudally in serial sections the roots of the vagus-spinal accessory complex, one notices a gradual marked decrease in the number of fibers which end in the nucleus of the tractus solitarius and a striking increase in the fibers which arise from the dorsal nucleus of the vagus and the nucleus ambiguus (figure). In sections through the level of the middle of the inferior olivary nuclei one sees few, if any, fibers entering the nucleus of the tractus solitarius, practically all of the fibers arising either from the dorsal nucleus of the vagus or the nucleus ambiguus.

COMMENT

It is possible that some of the cells just dorsal to, or in the region of, the nucleus of the tractus solitarius represent cells of the lateral (sensory) portion of the dorsal nucleus of the vagus, as described by Marburg [3] and others. However, it was not possible in the thionine preparations to separate clearly these two cell groups. Moreover, it is now believed that all visceral afferent fibers of the vagus nerve terminate in the nucleus of the tractus solitarius,[4] the dorsal nucleus of the vagus giving rise to efferent (general visceral) fibers.

The main component of the glossopharyngeal nerve terminates in the nucleus of the tractus solitarius and is, therefore, sensory. In addition, however, there is a motor component which arises from the region of the dorsal nucleus of the vagus, and probably the nucleus ambiguus, and which is represented by the smaller ventromedial root. The sensory and motor roots are usually separated at their sites of superficial origin from the medulla.

The main cephalic portion of the vagus-spinal accessory complex presents nerve fibers which terminate for the most part in the nucleus of the tractus solitarius; it is, therefore, chiefly sensory. The main caudal portion of the vagus-spinal accessory complex, as well as a small ventromedial portion of the cephalic roots, arises almost entirely from

3. Marburg, O.: Mikroskopisch-topographischer Atlas des menschlichen Zentralnervensystems, ed. 2, Leipzig, Franz Deuticke, 1909; ed. 3, 1927.

4. Ranson, S.: The Anatomy of the Nervous System, ed. 6, Philadelphia, W. B. Saunders Company, 1939.

the dorsal nucleus of the vagus nerve and the nucleus ambiguus. These are, therefore, chiefly motor. These conclusions are essentially in agreement with those of Foley and DuBois in their work on the cat.[5] It is not yet possible in the human brain to state the approximate relative proportions of sensory and motor roots or fibers within the total vagus-spinal accessory complex, as has been done in the cat by Foley and DuBois.[6] There is no clearcut demarcation between the cephalic, chiefly sensory, roots and the caudal, chiefly motor, roots.[7] A gradual transition between these two types of roots occurs.

CONCLUSIONS

As a result of tracing nerve fibers in serial sections from the nerve root to the nucleus of origin or of termination in the brain stem, it is possible to corroborate the following conclusions which were made on the basis of previous study of the glial structure of nerve roots:

1. The glossopharyngeal nerve presents a large sensory and a small ventromedial motor root, usually distinct at its origin from the medulla.

2. The main cephalic portion of the vagus-spinal accessory complex is chiefly sensory, the caudal portion being chiefly motor; the delicate roots which occur ventromedial to the large cephalic roots are also motor.

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5. Foley, J., and DuBois, F.: An Experimental Study of the Rootlets of the Vagus Nerve in the Cat, J. Comp. Neurol. **60**:137, 1934.

6. DuBois, F., and Foley, J.: Experimental Studies on the Vagus and Spinal Accessory Nerves in the Cat, Anat. Rec. **64**:285, 1936; Quantitative Studies of the Vagus Nerve in the Cat, J. Comp. Neurol. **67**:49, 1937.

7. The conclusion as to the predominantly sensory nature of the main cephalic portion of the vagus-spinal accessory complex was verified in 3 cases at operation. The results of these experiences will be dealt with in a later publication.

EFFECTS OF ANOXIA INDUCED BY NITROGEN INHALATION IN TREATMENT OF PSYCHOSES

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At the outset, insulin and metrazol as agents in the treatment of the psychoses have had the support only of a tenuous and empiric rationale. Statistical compilations of clinical impressions have, of necessity, sufficed. Nevertheless, efforts to supply an adequate physiologic explanation have not been wanting. Data have been accumulated from various sources [1] and have been interpreted as tending to show that during narcosis therapy, hypoglycemia and metrazol convulsions the brain is subjected to oxygen want. From such considerations it is not a far step to a general theory proposing interference with exchange of oxygen in the brain as the effective agent common to these therapeutic technics.[2]

METHOD

Himwich, Alexander and Lipetz [3] have described a method to produce anoxia by diluting the oxygen in the stream of the respiratory gases with nitrogen. With slight modifications, their technic was employed to produce a short, rapidly induced period of acute anoxia. A second technic was devised to maintain a prolonged period of partial anoxia over a fifteen minute interval. These technics were conducted in the following manner: An inhalator for surgical anesthesia, con-

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1. Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Brain Metabolism During the Hypoglycemic Treatment of Schizophrenia, Science **86**: 271 (Sept. 17) 1937.

2. Gerard, R. W.: Anoxia and Neural Metabolism, Arch. Neurol. & Psychiat. **40**:985 (Nov.) 1938. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, ibid. **40**:125 (July) 1938.

3. Himwich, H. E.; Alexander, F. A. D., and Lipetz, B.: Effect of Acute Anoxia Produced by Breathing Nitrogen in the Course of Schizophrenia, Proc. Soc. Exper. Biol. & Med. **39**:367 (Nov.) 1938. Himwich, H. E., and Alexander, F. A. D.: Nitrogen Inhalation Therapy for Schizophrenia: Preliminary Report on Technique, Am. J. Psychiat. **96**:643 (Nov.) 1939.

sisting of a well fitting face mask, a soda lime canister and a 5 liter capacity rubber rebreathing bag, was connected to an oxygen and nitrogen supply equipped with meters to gage the gas flow. An adjustable outlet on the rebreathing bag allowed either an entirely closed system for total rebreathing or a semiclosed system for partial rebreathing. The exchange of gases in the system was as follows:

1. Inhalation from the bag through the canister and exhalation through the canister into the bag.
2. Introduction of nitrogen or oxygen through the delivery tube connected directly with the mask.
3. Removal of carbon dioxide by chemical action of soda lime as the respired gases pass through the canister.
4. Escape of nitrogen, through the bag outlet, which served to sweep out the oxygen originally present in the respiratory tract.
5. Leakage around the mask, which might occur occasionally as a result of movement or struggling of the patient. This was in an outward direction because of a slight positive pressure in the system.

In the short method the rebreathing bag was partially opened, the flow of nitrogen started at the rate of 1 to 2 liters per minute and the mask held firmly to the face without strapping. The flow of nitrogen was then increased to a rate at which the rebreathing bag was distended and a flow maintained through the opening, usually 15 liters per minute. The administration was continued to the point of flexor spasm, extensor rigidity or opisthotonos, unless apnea was impending or alarming circulatory reactions appeared before these signs. Several liters of oxygen quickly introduced into the system terminated the treatment. The duration of the inhalations varied from ninety to one hundred and fifty seconds and averaged about two minutes. The time was remarkably constant for a given patient throughout the entire course of treatment. In 3 cases this technic was modified so that the total duration of inhalation averaged six minutes and the duration of anoxia, as judged by the signs noted, averaged five minutes. This was done by adding 150 cc. of oxygen per minute to the nitrogen and gradually reducing the oxygen to zero. The addition of oxygen to the inhalator prior to the initiation of nitrogen, recommended by the originators of the technic, prolongs the total duration of the inhalation. The omission of this step has little influence on the time interval measured from the appearance of early signs of anoxia to the termination of the inhalation.

In the prolonged technic total rebreathing was employed. The mask was held securely to the face with a head strap to insure a completely closed system. A continuous flow of oxygen of one-half the estimated metabolic requirement was supplied. Nitrogen in small amounts was added from time to time to maintain the desired depth of anoxia as determined by the circulatory, respiratory and neurologic reactions of the patient. In this technic, effort was made to reach a total of fifteen minutes' inhalation of an atmosphere low in oxygen.

THE RAPID METHOD

Physiologic Disturbances Incident to Anoxia.—1. Circulatory: The pulse rate increased to a maximum of from 150 to 170 per minute. The

systolic blood pressure increased from 20 to 50 mm. of mercury, without consistent changes in the diastolic tension. There was progressive fading of the heart sounds during the induction phase. Cardiac sounds were further obscured in the later stages, owing to the increased and irregular sounds from skeletal muscle activity. The intensity of heart sounds returned to normal promptly with administration of oxygen. An apical systolic murmur was heard frequently during the induction period and persisted for a minute or less after termination of treatment. An aortic diastolic murmur was heard rarely. In several cases a coupled beat, or gallop rhythm, was heard during the induction phase. Tachycardia, with a rate of from 100 to 110, persisting between sessions and for several days after the conclusion of a series of inhalations, was almost invariably observed. On 22 occasions electrocardiographic tracings were obtained during and after the inhalation. During the period of maximal anoxia the tracings were invariably obscured by skeletal muscle activity. Prior to this phase and after administration of oxygen the following changes were observed—premature auricular contractions, shifting pacemaker and depression of the T wave.

2. Respiratory: Irregular breathing, followed by hyperpnea, and later convulsive respiratory efforts were the usual responses. In deep anoxia respiration was stertorous and noisy. Invariably at the conclusion of the treatment the mouth was filled with thick saliva and mucus. Apnea of several seconds' duration was frequent after the initial inspiration of oxygen, due probably to release of the anoxemic stimulus mediated through the carotid body. This apnea was followed by hyperpnea, which lasted several minutes and was manifested by a regular rate, but an increased minute volume exchange. This is suggestive of an "oxygen debt."

3. Neurologic: (*a*) Motor signs. There were restless movements; often feeble, rarely strong, attempts to dislodge the mask; crossing and uncrossing of the legs; running movements, or simpler clonic phenomena. Ultimately, there occurred flexion of the hands and feet; pronation of the arms, with torsion movements, particularly of the upper extremities; occasional extension at the knees and elbows, with all four limbs rising into a stiff quadrupedal posture which suggested decerebrate rigidity. Opisthotonos was observed frequently. (*b*) Reflexes. Abdominal reflexes were diminished and sometimes had disappeared. Clonus was observed occasionally and the extensor plantar responses were elicited rarely. (*c*) Pupils. The pupils were dilated and fixed at the height of anoxia. There was immediate return of activity with restoration of oxygen. (*d*) Consciousness. This was

lost over an estimated period of approximately sixty seconds. Patients classified clinically as disturbed frequently offered physical resistance to the treatment. Others complained mildy, but not regularly, of a sense of suffocation, which did not seem to cause great discomfort.

4. Cutaneous: Ashen gray cyanosis invariably appeared, but was never an index of the severity of the anoxia. After the restoration of oxygen irregular and rapidly changing red blotches appeared over the forehead, the upper part of the chest and the neck. Sweating was rarely observed.

5. Gastrointestinal: The patients had fasted for ten hours or more. There was notable absence of nausea and vomiting.

Complications and Unusual Reactions.—1. Cardiac: Occasionally, auscultation revealed a sudden change in heart rate from 140 or 160 to 70 or 80 a minute. In such instances oxygen was always given without delay. In 2 instances (cases 14 and 18) the heart rate did not rise above 110. This unusual response was thought to indicate an unfavorable physiologic reaction and served as a basis for conservative treatment in these 2 cases. One patient, a psychoneurotic person, complained of pain in the chest; anxiety became so great that inhalations were discontinued after the third session. In no instance was there precordial pain. One patient (case 1) showed auricular fibrillation after the thirty-eighth inhalation. This persisted for seventy-two hours, then subsided spontaneously. The patient subsequently received a course of insulin therapy, with no cardiac complications.

2. Respiratory: These were perhaps the most alarming. In 10 instances in the entire series apnea was observed when the therapy was continued accidentally beyond the desired end point of flexor spasm. This apnea, which lasted from ten to thirty seconds, was associated with severe laryngeal spasm, intense cyanosis and inaudible or distant heart sounds of slow rate. Respiration was restored in all cases by insufflation of oxygen, with the aid of pressure manipulations of the rebreathing bag. A stiff intratracheal catheter and laryngoscope were at hand for such occasions should the spasm and apnea persist, but they were never used. After such an episode of prolonged apnea the patient usually remained dazed and restless for several minutes. Aphasia was never observed. After recovering consciousness the patient usually expressed fear and realized that something unusual and distressing had happened. A mild febrile reaction of 100 to 101 F.

usually followed. In 1 instance a subconjunctival hemorrhage appeared in the right eye.

3. Miscellaneous: In several patients urinary incontinence was observed. The greatest number of times that this occurred was ten in 24 inhalations (case 8), twelve in 50 inhalations (case 15), six in 50 inhalations (case 4) and five in 50 inhalations (case 10). Incontinence was also noted in 2 other single instances. It was most often seen at the height of anoxia, although in a number of instances it appeared during the phase of muscular relaxation following the restoration of oxygen. Fecal incontinence occurred on 1 occasion when the anoxia was prolonged beyond the desired end point. One patient, after a single period of inhalation, complained of a severe muscle cramp in the left leg.

THE PROLONGED METHOD

Physiologic disturbances incident to anoxia by the prolonged method were strikingly different from those observed with the short method. After a period of restlessness lasting from three to four minutes, the patient passed into a quiet unconscious state, which was maintained at an even level until oxygen was supplied. Respiration was irregular and increased in rate and depth during the restless phase. During the latter part of the anoxia respiration became regular and stertorous, with forceful prolongation of expiration. The apnea following administration of oxygen was more prolonged than with the short method, lasting five seconds or more. The blood pressure rose initially and then returned to a maintenance level approximating that of the patient's normal pressure. After restoration of oxygen there were an immediate and abrupt rise in systolic pressure to 150 mm. or more and a fall in diastolic pressure of approximately 20 mm., which persisted from three to five minutes. The extensor spasms and torsion phenomena were not observed during these inhalations, but the pupils were fixed. Oxygen was usually withheld until a total inhalation period of fifteen minutes had elapsed. In several instances a rise or rapid variations in heart rate or a sudden drop in blood pressure necessitated earlier termination. After 10 daily administrations in each of 2 patients (cases 23 and 24) the procedure was abandoned because of its potential dangers. Laboratory determinations of the oxygen, carbon dioxide and dextrose contents of arterial and of venous blood were made in these 2 cases during treatment.[4] The protocols of the treatments, together with the laboratory data, follow.

4. Dr. Walter Goldfarb made the gas determinations on the blood.

Patient A. D'A. Nitrogen Treatment No. 7

Time 11/20/39	Duration, Min.	Pulse Rate	Blood Pressure, Mm. of Mercury	Comment
8:00 a. m.		90		
10:30 a. m.	0:00	120	140/90	
	1:00	120		Restless
	2:00	120	160/90	Restless
	3:00	140	170/120	Restless
	4:00	140	150/110	
	5:00	140		Quieter; moaning sounds with inspiration and expiration
	6:00	140	160/110	Quiet; moaning sounds with inspiration and expiration
	7:00	140	140/110	Quiet *
	8:00	140	150/100	Quiet; moaning sounds with inspiration and expiration
	9:00	150	120/90	Quiet; moaning sounds with inspiration and expiration
	10:00	150	130/100	Quiet; A-V differences
	11:00	150	150/90	Quiet *
	12:00	150	150/90	Quiet; moaning sounds with inspiration and expiration
	13:00	150	150/100	Quiet; moaning sounds with inspiration and expiration
	14:00	150		
	15:00	150	150/90	
	15:15			Oxygen
	16:00	160	150/100	Names eyebrow; responses slow
10:47 a. m.	17:00	170	150/90	Groaning
	19:00	160	140/90	"I groan because it makes me feel better. The pressure went down to my feet."
	21:00	160	120/70	"I have pains in my stomach."
	24:00	150	130/70	
10:59 a. m.		120	105/80	Quiet; eyes closed
4:20 p. m.		84		
8:00 p. m.		108		

Chemical Determinations Before Inhalation

	Arterial Blood	Blood from Internal Jugular Vein
Oxygen	17.7 vol. %	11.7 vol. %
Carbon dioxide	46.3 vol. %	53.7 vol. %
Dextrose	125 mg. per 100 cc.	108 mg. per 100 cc.

11:20 a. m.	0:00	120	140/90	

Chemical Determinations During Inhalation

	Arterial Blood	Blood from Internal Jugular Vein
Oxygen	4.7 vol. %	2.8 vol. %
Carbon dioxide	30.7 vol. %	29.2 vol. %
Dextrose	134 mg. per 100 cc.	138 mg. per 100 cc.

* Oxygen in samples from rebreathing bag (average), 3.8 vol. per cent.

Patient L. A. Nitrogen Treatment No. 7

Time 11/20/39	Duration, Min.	Pulse Rate	Blood Pressure, Mm. of Mercury	Comment
8 : 00 a. m.		90		
10 : 02 a. m.	0 : 00	90	150/80	Quiet
	1 : 00	120	130/90	Quiet
	2 : 00	120	120/80	Quiet
	3 : 00	130	118/80	Quiet
	4 : 00	140	120/90	Restless
	5 : 00	140		Restless
	6 : 00	120		Restless
	7 : 00	130	120/80	Restless
	8 : 00	130	120/80	Restless
	9 : 00	120		Restless *
	10 : 00	120		Quiet
	11 : 00	100	100/90	Quiet
	12 : 00	120	150/80	Quiet *
	13 : 45	120	130/90	Quiet; A-V differences
	15 : 00	120	130/80	
	15 : 25			Oxygen
	16 : 00	130	150/90	
	17 : 30	120	150/80	Moaning; restless
	18 : 20	110	130/80	Names eyebrow
10 : 22 a. m.	20 : 00	120	130/90	Quieter; still moaning
10 : 55 a. m.		80	110/80	Apathetic; quiet
4 : 00 p. m.		80		
8 : 00 p. m.		88		

Chemical Determinations Before Inhalation

	Arterial Blood	Blood from Internal Jugular Vein
Oxygen	17.4 vol. %	15.6 vol. %
Carbon dioxide	50.6 vol. %	49.6 vol. %
Dextrose	108 mg. per 100 cc.	103 mg. per 100 cc.

Chemical Determinations During Inhalation

	Arterial Blood	Blood from Internal Jugular Vein
Oxygen	2.4 vol. %	2.4 vol. %
Carbon dioxide	35.7 vol. %	36.3 vol. %
Dextrose	153 mg. per 100 cc.	132 mg. per 100 cc.

* Oxygen in samples from rebreathing bag (average), 3.9 vol. per cent.

RESULTS

A summary of the cases, including age of the patients, diagnosis, duration of illness, number of inhalations and condition after treatment, is found in the accompanying table. The condition of the patients after treatment was classified according to the groupings generally used for reporting the results of insulin and metrazol therapy. Twenty-four patients received a total of 1,024 inhalations. Of these, 19 received the short treatment; 3 (cases 8, 11 and 15), the modified short treat-

ment, and 2 patients (cases 23 and 24), the prolonged treatment. Nine patients received insulin—2 of them prior and 7 subsequent to treatment with nitrogen. Conclusions must be tentative as the number of cases is small, although the series has the merit of persistence to a large number

Summary of Clinical Data

Case No.	Patient	Sex	Age	Diagnosis	Duration of Illness, Mo.	No. of Inhalations	Condition After Treatment	Comment
1	J. F.	M	27	Catatonia	24	38	Unimproved; group 4	Auricular fibrillation developed; no improvement after insulin
2	F. R.	M	27	Paranoia	13	42	Unimproved; group 4	Previous improvement with insulin
3	R. V.	M	13	Hebephrenia	12	32	Slightly improved; group 3	Failure to return for treatment
4	J. S.	M	28	Paranoia	24	50	Unimproved; group 4	Discharge after insulin treatment; group 2
5	B. T.	M	22	Hebephrenia	60	50	Unimproved; group 4	Previous improvement with insulin
6	E. O'B.	M	19	Hebephrenia	18	50	Unimproved; group 4	Transfer to state hospital
7	M. S.	F	29	Anxiety neurosis	96	50	Unimproved; group 4	Return home; adjustment unchanged
8	W. S.	M	15	Catatonia	6	24	Slightly improved; group 3	Failure to return for treatment
9	V. D'V.	F	16	Catatonia	3	50	Unimproved; group 4	Transfer to state hospital
10	J. S.	M	29	Paranoia	4	50	Slightly improved; group 3	Discharge after insulin treatment; group 2
11	M. S.	F	23	Paranoia	15	50	Unimproved; group 4	Transfer to state hospital
12	P. G.	M	29	Paranoia	18	50	Unimproved; group 4	Group 4 after insulin; transfer to state hospital
13	A. P.	M	15	Paranoia	72	50	Unimproved; group 4	Discharge after insulin treatment; group 4
14	R. A.	F	32	Manic-depressive depression	4	25	Slightly improved; group 3	Treatment discontinued because of cardiac response; discharge
15	W. M.	M	22	Catatonia	12	51	Unimproved; group 4	Discharge after insulin treatment; group 3
16	A. F.	M	21	Paranoia	1	51	Unimproved; group 4	Group 4 after insulin treatment
17	M. V.	F	25	Manic-depressive depression	1	13	Unimproved; group 4	Marked disturbance; transfer to state hospital
18	A. K.	F	33	Manic-depressive depression	6	20	Improved; group 4	Failure to return for reexamination
19	A. H.	F	33	Paranoia	18	28	Unimproved; group 4	Failure to return for treatment
20	A. K.	F	36	Manic-depressive depression	2	36	Unimproved; group 4	Transfer to private hospital
21	H. J.	F	17	Paranoia	9	50	Improved; group 2	Home; adjustment good
22	B. P.	F	18	Hebephrenia	1	50	Unimproved; group 4	Transfer to state hospital
23	L. A.	F	18	Catatonia	18	32	Unimproved; group 4	Ten prolonged inhalations; transfer to state hospital
24	A. D'A.	F	19	Hebephrenia	30	32	Unimproved; group 4	Ten prolonged inhalations; transfer to state hospital

of inhalations for each patient. Observation of the patients from day to day and from week to week during the course of the inhalations gave the impression of monotonous sameness. There seemed to be little change in the subjective attitudes and objective behavior and adjust-

ments of the patients. Five patients failed to return for continuation of treatments or for reexamination. Because of the absence of noticeable improvement, it was often difficult to maintain the cooperation of relatives. In no case did a patient acquire adequate insight. During the course of insulin treatments, a patient (case 15), with catatonic symptoms, usually had a "lucid" period of from ten to thirty minutes' duration after termination of hypoglycemia. At no time during his course of nitrogen inhalations did he show this response.

SUMMARY

Twenty-four patients, 19 of whom had conditions which were classified as schizophrenia, 4 as manic-depressive depression and 1 as anxiety neurosis, were subjected to anoxia by means of nitrogen inhalation. The reaction of these patients from the clinical psychiatric standpoint was strikingly neutral, and the lack of response in this limited group has not compared favorably with expectations on the basis of experience with insulin and metrazol in similar cases.

The effects of inhalations on the circulatory and respiratory systems were noted.

The neurologic manifestations consisted essentially of transient decerebrate rigidity.

This experience with anoxia directly induced tends to cast doubt on the theory that interference with oxygen metabolism is the modus operandi of insulin and metrazol treatments.

NEUROPATHOLOGIC STUDY OF SIX CASES OF PSYCHOSES IN WHICH METRAZOL WAS USED

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Since the publication of the experimental study on the effect of metrazol injections on the rabbit brain,[1] by this method several deaths following the treatment of psychotic patients have been reported. Kraus,[2] who gave injections of metrazol to 64 patients, observed 2 cases of death with abscess of the lung eight and ten days, respectively, after the last injection. A woman who had not shown roentgenographic changes in the lung nine months before the treatment began received six injections, which were followed by shock; tuberculous pneumonia developed. Van de Graaf, van Montfrans and Brouwer [3] reported 4 cases of pneumonia following treatment; they considered the possibility that the injections of metrazol might have activated pulmonary tuberculosis. In the American literature, Hayman and Brody [4] reported a case in which death followed six injections, with a total of 27 cc. of metrazol. They observed that the brain was enlarged, edematous and markedly congested; "the individual nerve cells showed no abnormalities." Petersen [5] added to the German literature the autopsy reports in 2 cases, in which there was generalized ischemic disease of ganglion cells with shadow cell formation and diffuse gliosis, prevalent in the central

Read at a meeting of the Chicago Neurological Society, April 18, 1940.

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1. Liebert, E., and Weil, A.: Histopathologic Changes in the Brain Following Experimental Injections of Metrazol. Arch. Neurol. & Psychiat. **42**:690 (Oct.) 1939.

2. Kraus, G.: Komplikationen bei der Kardiazol-Behandlung nach Meduna, Psychiat. en neurol. bl. **42**:81, 1938; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **90**:452, 1938.

3. van de Graaf, A. J.; van Montfrans, G., and Brouwer, G.: Pulmonary Complications During Metrazol Therapy of Psychoses, Nederl. tijdschr. v. geneesk. **28**:4078 (Aug. 20) 1938.

4. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Report of Fatal Case with Autopsy, J. A. M. A. **112**:310 (Jan. 28) 1939.

5. Petersen, F.: Beobachtungen und Erfahrungen bei der Behandlung der Schizophreine mit Cardiazol, Allg. Ztschr. f. Psychiat. **111**:366, 1939.

region. Jansen and Waaler [6] studied the brain in a case of dementia praecox after injection of 50 cc. of metrazol. They observed bilateral softening of the frontal lobes and perivascular lymphocytic infiltration, together with scattered glial foci.

Unfortunately, with the exception of Petersen and Jansen and Waaler, none of these authors made detailed neurohistopathologic studies, and observations on the glia were altogether neglected.

To this limited number of autopsy reports are added those in 6 cases of psychoses in which the patients had previously been treated with injections of metrazol and had survived for from two to ten months after the last injection. Four patients died of pulmonary tuberculosis, 1 of cardiovascular-renal disease and the sixth of bronchopneumonia with purulent bronchitis. In carrying out the histopathologic study of the brains in such cases, one must be conscious of the many difficulties and fallacies inherent in such a task. Not only the pathologic changes due to the underlying primary psychosis but the lesions superimposed by age and the ravages of the final lethal disease must be evaluated. Only after these have been discounted may one proceed to study the effect of the metrazol injections. Again, one must distinguish between the changes seen in cases in which death occurred during the treatment and those which are observed after a period of survival following discontinuation of treatment. We have previously pointed out, in a study of experimental injections of metrazol,[1] the difference in the pathologic picture in these two groups.

We agree with Spielmeyer that pathologic lesions specific for dementia praecox do not exist. The vague and nonspecific changes in the ganglion cells and the diminution in the number of neurons in larger islands throughout the cerebral cortex, which were emphasized by Fünfgeld, Miskolczy, Naito, Josephy and others, have been recently critically compared by Peters [7] with the observations in the central nervous system of executed persons who were not psychotic. He came to the conclusion that irregular distribution of neurons with apparent diminution in the number of circumscribed islands is also common in the brains of normal persons. There now is unanimity of opinion as to the normal condition of the astroglia in dementia praecox. Alzheimer's description of an increase in fibrous glia at the borderline of the gray and the white matter has not been confirmed by others as specific for dementia praecox.[8]

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6. Jansen, J., and Waaler, E.: Pathologisch-anatomische Veränderungen bei Todesfällen nach Insulin-und Cardiazolschockbehandlung, Arch. f. Psychiat. **111**:62, 1940.

7. Peters, G.: Zur Frage der pathologischen Anatomie der Schizophrenie, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:361, 1937.

8. Alzheimer, A.: Beiträge zur pathologischen Anatomie der Hirnrinde und zur anatomischen Grundlage einiger Psychosen, Monatschr. f. Psychiat. **2**:90, 1897.

The pathologic changes of old age have been excluded in our cases by selecting the brains of 3 schizophrenic patients who were 18, 28 and 39 years of age, respectively. For evaluation of the possible influence of the final tuberculous process, brains from psychotic and nonpsychotic patients who had died of tuberculosis were studied.

REPORT OF CASES

A. *Dementia Praecox, with Pulmonary Tuberculosis.*—CASE 1.—In L. M., a white man aged 28, a psychosis began with catatonic symptoms at the age of 21. He thought that he was Jesus Christ; he became antagonistic, especially toward his stepmother, and was uncooperative.

On admission to the Elgin State Hospital in 1937 he weighed only 70 pounds (31.8 Kg.). He had been treated with four injections of metrazol when, in January 1938, roentgenograms of the chest indicated a beginning tuberculous process in the left lung. Pneumothorax was produced in April 1938, but the patient continued to lose weight. No improvement in the mental condition was noted.

The patient died on Aug. 5, 1938, and autopsy performed four hours later, revealed extensive tuberculosis of the entire left lung and the upper lobe of the right lung. The brain weighed 1,340 Gm., and showed no gross pathologic changes.

CASE 2.—J. K., a white man aged 39, who was admitted to the Elgin State Hospital in 1933, exhibited crying spells, paranoid ideas and auditory hallucinosis. During his residence at the hospital he rarely talked. During 1934 he seemed to improve slightly and worked on the farm. In January 1937 his behavior changed and he showed marked catatonic symptoms.

Between Aug. 3, 1937 and May 10, 1938 he received a total of 500 cc. of metrazol. After treatment he remained negativistic, but tube feeding could be discontinued. In June 1939 high fever with diarrhea developed; he died two months later.

Autopsy was performed three hours after death. The anatomic diagnosis was tuberculosis of the right lung, with cavity formation in the apex; tuberculous ulcers in the small and large intestines, and decalcification of the fourth, fifth and sixth dorsal vertebrae.

CASE 3.—O. Q., a white youth aged 18, had an illness that was diagnosed as hebephrenic dementia praecox. The first mental symptoms had been observed at the age of 16, when he expressed ideas of inferiority and hallucinated freely.

Treatment with metrazol was started in July 1937 and was discontinued in January 1938, after fifty-three injections had been given. There was slight improvement in his condition. After combined treatment with ten injections of typhoid vaccine and metrazol in March, he appeared somewhat less restless and more cooperative. In November 1938 roentgen examination revealed diffuse mottling throughout both lungs. The patient died on Feb. 22, 1939, of rapidly progressing tuberculosis. Autopsy showed extensive bilateral pulmonary tuberculosis and tuberculosis of both kidneys.

B. *Manic-Depressive Psychosis, with Pulmonary Tuberculosis.*—CASE 4.—A. R., a Negress aged 25, was admitted to the hospital twice, first in 1932 and again in 1934. Each time she was discharged after several months. She made a fair adjustment until March 1938, when she again became severely depressed. Metrazol treatment was instituted in August, with some improvement. A total of thirteen injections was given.

In November 1938 a bilateral exudative pulmonary tuberculosis was found. The patient died on April 12, 1939. There were extensive tuberculosis with cavity formation in the left lung, tuberculous bronchopneumonia in the right lung and many tuberculous ulcers in the cecum.

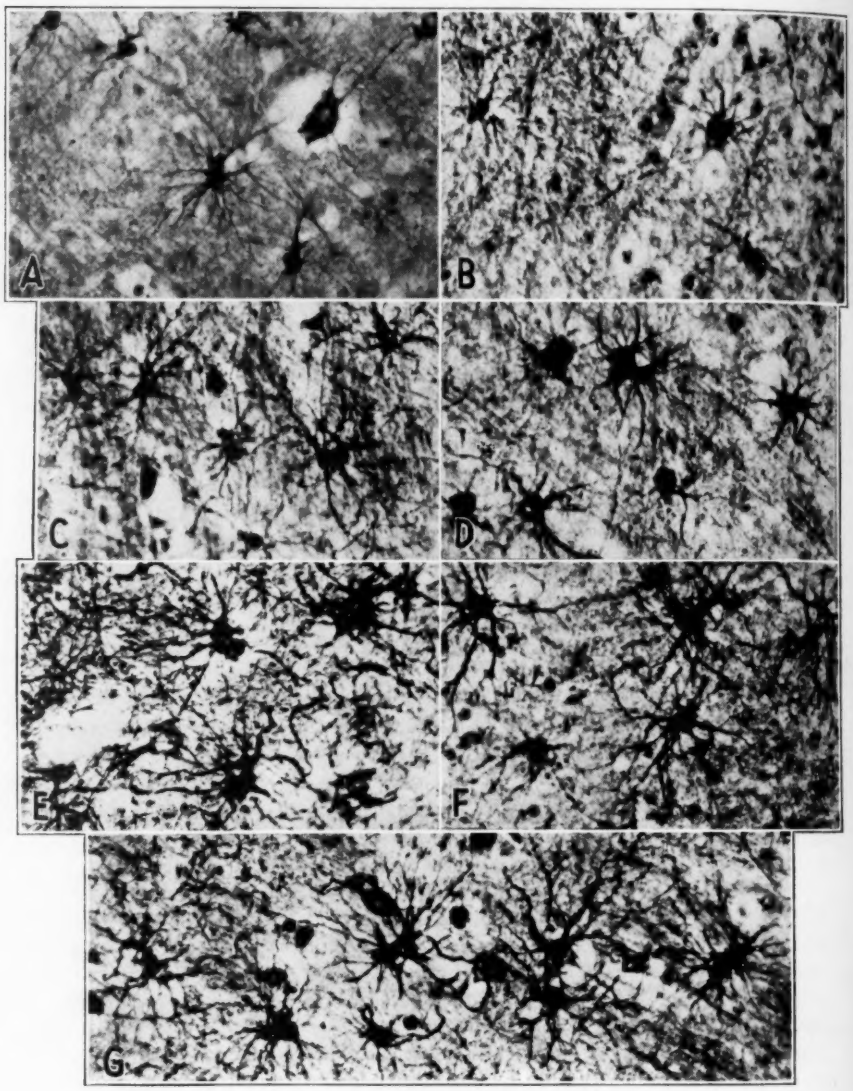

Figure 1

(See legend on opposite page)

C. *Involutional Psychosis.*—CASE 5.—M. S., a white woman aged 49, had been admitted to the hospital ten years before, when she had an attack of depression lasting three months. In 1935, at the age of 45, there began another period of depression, with marked agitation and numerous attempts of suicide.

Treatment with metrazol was started in May 1938. A total of twenty-seven injections was given. For a short time there was marked improvement, soon followed, however, by relapse. The patient became increasingly dehydrated and died in September 1938. Autopsy revealed long-standing cardiovascular-renal disease, with coronary arteriosclerosis.

CASE 6.—S. C. M., a white woman aged 50, at the age of 40 had had an attack of depression, from which she recovered completely. At the age of 48 she again became depressed, gradually withdrew and had ideas of unworthiness.

Treatment with metrazol was begun on Aug. 11, 1938; eight injections were given. Although after the treatment she no longer needed to be fed with a tube, she was still combative, resistive and noncooperative. She died, three months after the last injection, of confluent bronchopneumonia and purulent bronchitis. These findings were confirmed at autopsy.

D. *Psychosis Without Metrazol Treatment.*—The first of 2 cases, that of a hebephrenic patient aged 21, who died of pulmonary tuberculosis, was selected for comparison with the cases in group A. The second case, that of a patient with organic disease of the brain and tuberculous meningitis, was selected as an extreme example of cerebral tuberculous meningitis in order to emphasize the contrast between the histopathologic changes in such a case and those in cases in which metrazol treatment was given; in the latter cases there was pulmonary tuberculosis but not tuberculous meningitis.

CASE 7.—Q. S., a white man aged 21, was admitted in 1936 with the diagnosis of dementia praecox of undetermined type. During his stay at the hospital he became more withdrawn, expressed bizarre delusional ideas and eventually became completely apathetic. In January 1939 hemoptysis occurred. The patient died four months later.

The anatomic diagnosis was bilateral pulmonary tuberculosis, intestinal tuberculosis and brown atrophy of the heart.

CASE 8.—A. B., a white man aged 43, was admitted to the Elgin State Hospital only seven days before death. He was confused and fearful. No further information was obtained. He died on April 22, 1938.

The anatomic diagnosis was tuberculosis of the right kidney and tuberculous leptomeningitis.

EXPLANATION OF FIGURE 1

Fig. 1.—Sections from the white matter at the borderline of the gray matter of the frontal cortex, area FD. (Cajal's gold chloride–mercury bichloride stain; magnification about 370). *A* and *B* are from cases in which no metrazol was given; *C* to *G*, from 5 cases in which treatment with metrazol was employed. In these 5 cases, varying degrees of hypertrophy and hyperplasia of the astroglia are shown, as compared with the more normal appearance in *A* and the very mild hypertrophy in *B*. *A* (case 8) is from a patient with tuberculous meningitis who was not treated with metrazol; *B* (case 7), from a patient with dementia praecox who was not treated; *C* (case 5), from a patient with involutional melancholia who was given a total of 203 cc. of metrazol by injection; *D* (case 2), from a patient with dementia praecox who was given a total of 500 cc. of metrazol; *E* (case 6), from a patient with involutional melancholia who was given a total of 48 cc. of metrazol; *F* (case 1), from a patient with dementia praecox who was given a total of 15 cc. of metrazol, and *G* (case 3), from a patient with dementia praecox who was given a total of 477 cc. of metrazol.

HISTOLOGIC STUDIES

Technic.—All brains were removed within six hours after death and fixed immediately in a solution of formaldehyde. Blocks from the following areas were selected: frontal lobe (FD and FA), parietal lobe (PE), occipital lobe (OA),

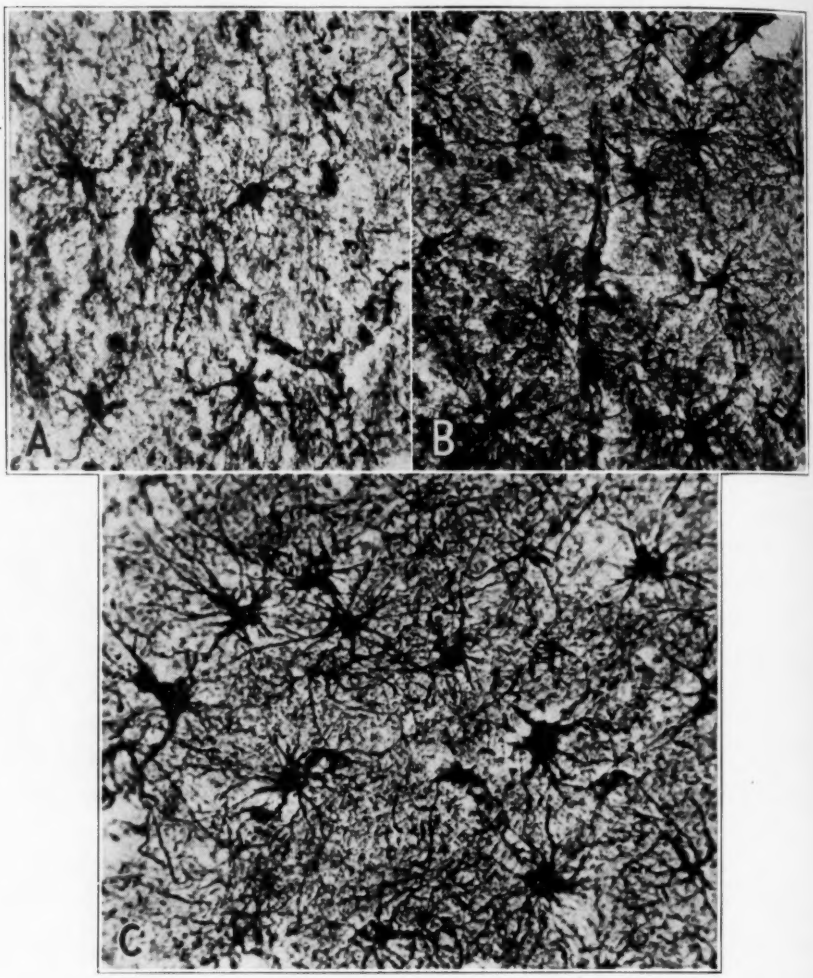

Fig. 2.—Sections from lamina 5 of the gray matter of the frontal cortex, area FD. The same technic was applied and the same magnification used as in the sections shown in figure 1. In these 3 cases in which metrazol was used in treatment, the hypertrophy and hyperplasia of the astroglia are pronounced. *A* (case 4) is from a patient with manic-depressive psychosis who was given a total of 61 cc. of metrazol; *B* (case 3), from a patient with dementia praecox who was given a total of 477 cc. of metrazol, and *C* (case 6), from a patient with involutional melancholia who was given a total of 48 cc. of metrazol.

striatum and gyrus hippocampi (HE and HF).[9] They were embedded in paraffin and pyroxylin and cut as frozen blocks. The cresyl violet, Van Gieson, Weil, Davenport, Bodian, del Río-Hortega (Kanzler modification), Cajal gold chloride–mercury bichloride and Holzer staining methods were applied.

Histologic Changes.—Case 1.—There was mild cellular infiltration of the pia-arachnoid over the convexities of the brain, consisting of lymphocytes intermingled with larger mononuclear cells, together with mild increase in collagenous connective tissue fibers. The neurons in all the sections studied appeared normal. There was diffuse increase in astrocytes of both the gray and the white matter in all sections, being somewhat more marked in areas FA and HE than in other regions. The hyperplasia and hypertrophy were most prominent in the protoplasmic astrocytes of the fourth and fifth cortical layers and in the fibrillary astrocytes of the underlying white matter of the cerebral cortex (fig. 1 *F*). In the center of the white matter the astrocytes had undergone clasmatodendrosis. The microglia did not show any proliferative changes. No vascular disease, hemorrhages or scars of preceding hemorrhages were detected.

Case 2.—Except for mild meningeal edema, cresyl violet preparations did not show any histopathologic changes. In sections stained by Cajal's gold chloride–mercury bichloride method there was a mild increase in the number and size of the astrocytes, the gray matter of the cerebral cortex being more affected than the white matter (fig. 1 *D*). In comparison, areas FD and FA were more affected than area OA. Glial proliferation was considerable in the various structures of the gyrus hippocampi, and was fairly marked also in the striatum. Mild hypertrophy of microglia corresponded in degree to the variations in the astrocytic proliferation.

Case 3.—In contrast to the picture in the 2 preceding cases, the neurons in this case were damaged throughout (fig. 5 *C*). In the cortical gray matter were seen many shrunken pyramidal cells with dark-staining nuclei, the membrane of which was folded. Many of the ganglion cells of the striatum were vacuolated, and in the hippocampus there was an increase in satellite cells associated with instances of neuronophagia. Hypertrophy and hyperplasia of astrocytes, too, were much more pronounced in this case than in the 2 preceding cases of dementia praecox, in which treatment with metrazol was given. In the fifth and sixth layers of the cerebral cortex the microscopic field seemed to be covered by a dense layer of proliferated astrocytes (figs. 1 *G* and 2 *B*). Sections through the gyrus hippocampi stained by the Holzer method revealed dense scars of fibrous glia in both area HE and area HF; other fibrous scars were seen in the subependymal tissue (fig. 4). The hypertrophy of the microglia also was more pronounced than in cases 1 and 2, though not as spectacular as the astrocytic proliferation (fig. 3 *C* and *D*).

Case 4.—The pia-arachnoid was mildly edematous, but not infiltrated with cells. A small hemangioma, measuring about 5 mm. in diameter and composed of dilated capillaries, lay in the midst of the reticular formation of the pons. Otherwise the gross appearance of the brain was normal. With the exception of mild ganglion cell disease in the frontal lobe, in the form of edema and granulation of the cytoplasm (with preservation of the nuclei), the neurons appeared normal (fig. 5 *B*). The astrocytic proliferation was mild in the cerebral cortex but marked in the gyrus hippocampus, more so in area HE than in area HF (fig. 2 *A*). There was only mild hypertrophy of microglia in this region.

9. The nomenclature used in designating these areas is that of von Economo.

Case 5.—The brain was rather small, weighing 1,120 Gm., but the configuration appeared normal. The vascular disease which had affected the heart and kidneys apparently had spared the brain, the vessels of which appeared normal.

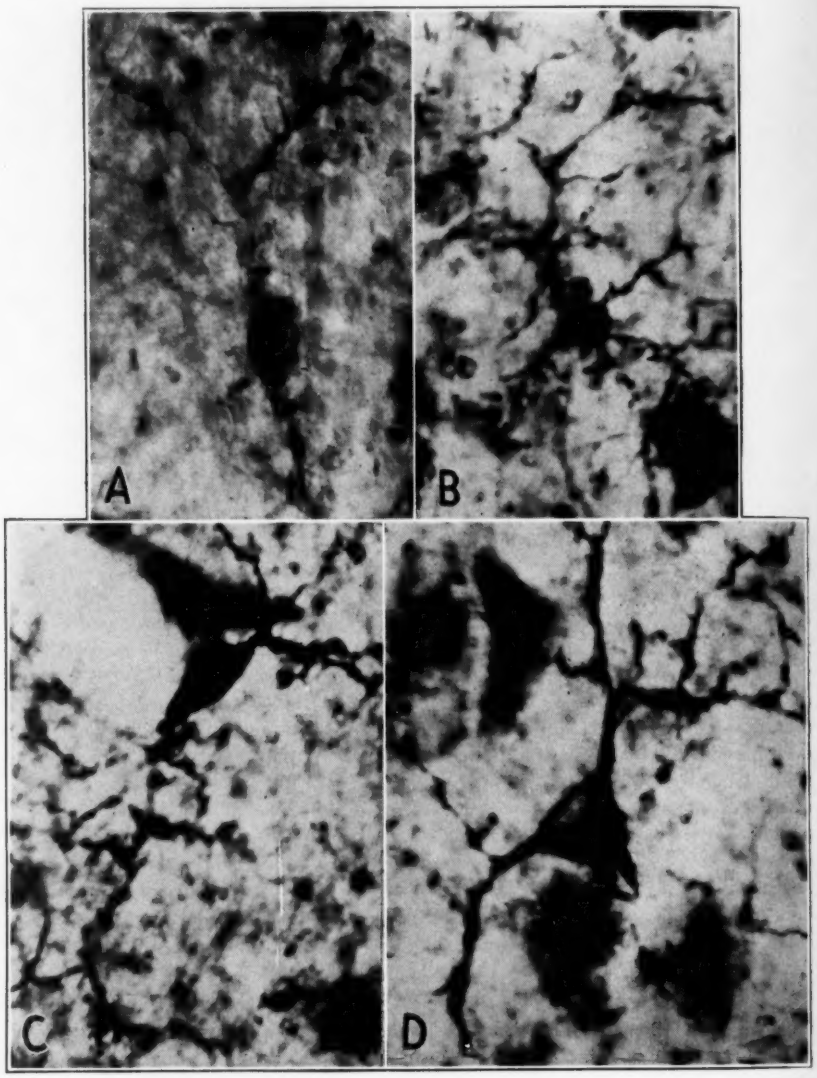

Fig. 3.—Sections of the gray matter of the frontal cortex, area FD (Kanzler's modification of del Rio-Hortega's method for microglia; magnification about 1,350). *A* and *B* (case 7) are from a patient with dementia praecox, who was not treated, and *C* and *D* (case 3), from a patient with dementia praecox who was given a total of 477 cc. of metrazol; the sections show marked hypertrophy of microglia.

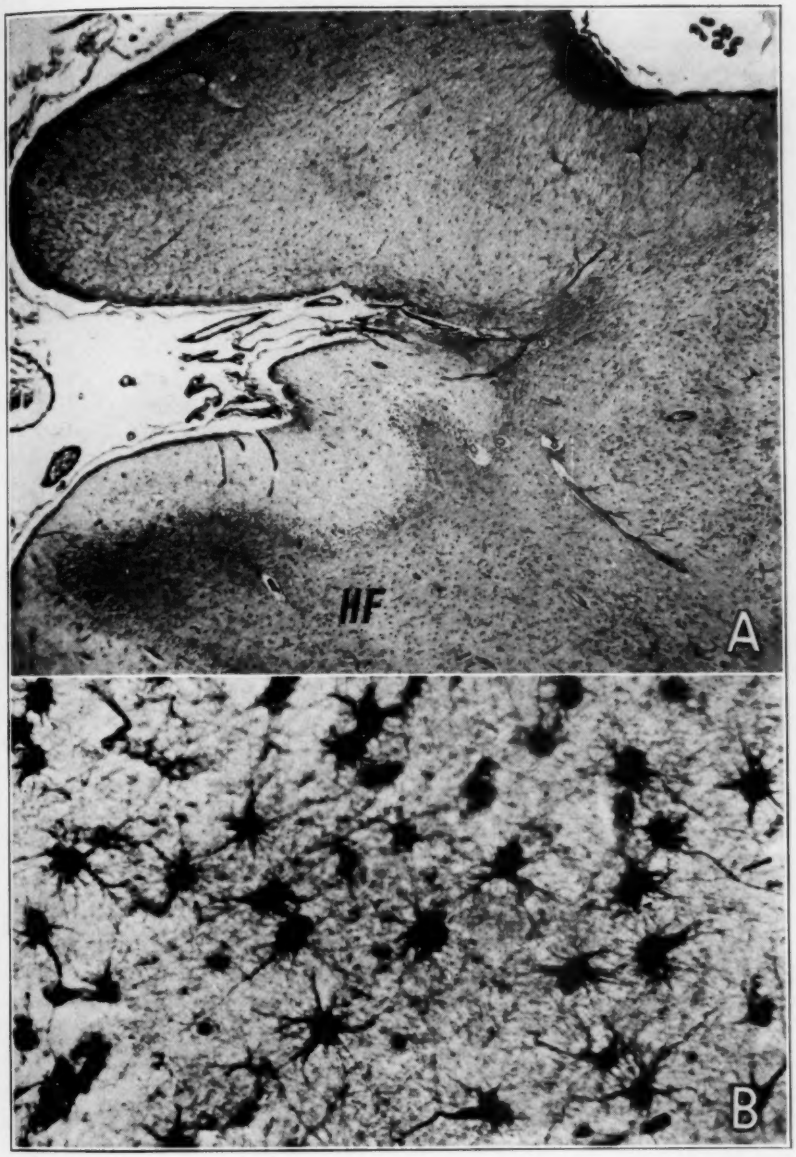

Fig. 4.—Sections from the gyrus hippocampus (*A*, Holzer stain, magnification 25; *B*, Cajal's gold chloride–mercury bichloride stain; magnification 370). Both sections are from case 3, one of dementia praecox, in which a total of 477 cc. of metrazol was injected. *A* shows the dense glial scar in the subependymal tissue of the inferior horn of the lateral ventricle (right upper corner) and the diffuse sclerosis of area HF of the cornu ammonis, and *B*, marked hypertrophy and hyperplasia of astrocytes in area HF.

The only exception was a small superficial area of anemic softening in area FD, which had been organized by a dense fibrous glial scar. Otherwise, no glial proliferation was observed, except for mild astrocytic hyperplasia in area HF. No ganglion cell disease was present (fig. 1 *C*).

Case 6.—The pronounced changes in the ganglion cells in this case were in in marked contrast to those in the 5 preceding cases. Grossly, the brain had not

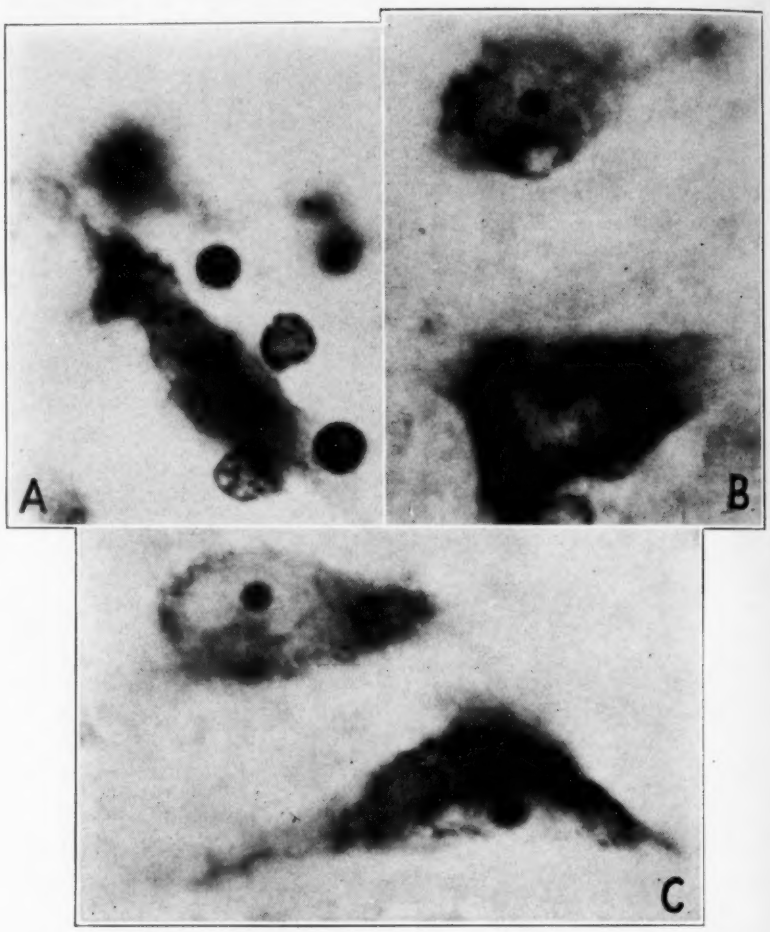

Fig. 5.—Sections from area FD, lamina 5 (cresyl violet stain magnification 1,700). *A* is a higher magnification of a cortical ganglion cell in case 6, one of involutional melancholia, in which a total of 48 cc. of metrazol was given. Severe disease of the neuron with beginning neuronophagia is shown. *B* is from case 4, one of manic-depressive psychosis, in which a total of 61 cc. of metrazol was injected. The two ganglion cells have undergone mild vacuolation only. *C* is from case 3, one of dementia praecox, in which a total of 477 cc. of metrazol was injected. The ganglion cells are severely diseased; their cytoplasm is shrunken, and their nuclei show folding of the membrane.

shown any abnormalities. The pia-arachnoid was transparent and did not present histologic changes. However, in sections stained with cresyl violet the neurons appeared diseased throughout the cortical gray matter and the nuclei of the brain stem. The cortical pyramidal cells were all shrunken and distorted; their dendrites were stained distinctly. Other neurons were mere shadows, or contained vacuoles and were edematous. Frequently, neuronophagia was seen, especially in the deeper layers of the cortex and in the striatum (fig. 5 *A*). Cajal gold chloride–mercury bichloride preparations revealed intense astrocytic hypertrophy and hyperplasia. In the cortical gray matter these changes in places surpassed even the intense reaction which has been described in case 3. The astrocytic response was not disseminated, but was diffuse and affected both the gray and the white matter (figs. 1 *E* and 2 *C*). In contrast to this marked response of the astroglia, the microglia showed no hypertrophy.

CASE 7.—The only histopathologic changes were mild edema of the pia-arachnoid covering the cortex, without cellular infiltration, and mild perivascular edema in the white matter of the cerebral cortex. In the Virchow-Robin spaces surrounding the vessels, isolated scavenger cells filled with a dark bluish pigment were seen. The glia in their environment formed a thin circular wall. Furthermore, there was mild hypertrophy of astrocytes in area HE (figs. 1 *B* and 3 *A* and *B*).

CASE 8.—The pia-arachnoid was somewhat hazy and thickened over the left frontal pole. At the base, the left frontal lobe was softened and covered with a thick rind of pia-arachnoid. Histologic examination revealed tuberculous meningitis and spreading of the tuberculous process into the outer layers of the underlying cortex. The pia-arachnoid covering the parietal and occipital lobes was only mildly infiltrated with small round cells and plasma cells. Progressive reaction of the astroglia was present only in the outer layers of the cortex, adjacent to the areas of tuberculous meningitis. The deeper layers presented a normal appearance, which was in marked contrast to the glial architectonics in the cases in which metrazol was used (fig. 1 *A*).

Myelin Stains.—Studies of sections stained for myelin sheaths have not been mentioned in the preceding reports because they did not reveal histopathologic changes. An exception occurred in case 8, in which there were substantial loss of myelin and destruction of axis-cylinders in the areas surrounding the tuberculous foci. Even in cases 3 and 6, in which the gliosis was marked, the finer myelinated fibers in areas 5 and 6 were well stained. Changes in the neurofibrils, as seen in preparations stained by the Bodian or Davenport method were proportional to the damage of the neurons. In case 3, agglutination, distortion and swelling of neurofibrils were seen in the larger pyramidal cells of the cerebral cortex, changes which were mild in case 4, although more pronounced in case 6. In the remaining cases no marked pathologic changes were noted.

COMMENT

In the accompanying tables are reviewed the clinical course and pathologic lesions in the 6 cases in which metrazol treatment was employed and in the 2 cases in which no such treatment was given. In table 2 the plus system of recording has been applied in the evaluation of histopathologic changes. Although this method is subjective, it allows, nevertheless, a fair comparison of the relative intensities of pathologic changes. In relation to astrocytes and microglia + indicates

the degree of hypertrophy and hyperplasia; in relation to neurons it designates the severity of the ganglion cell disease.

The outstanding feature of the histologic study is the hypertrophy and hyperplasia of the astroglia in 4 of the 6 cases in which treatment with metrazol had been employed. A comparison of the cases in which no treatment was given with other cases from our laboratory

TABLE 1.—*Clinical Course*

Case	Age	Sex	Clinical Diagnosis	Duration of Disease, Years	Metrazol		Survival, Mo.
					Number of Injections	Total Number of Cc.	
1	28	M	Dementia praecox (catatonic)	7	4	15	4
2	39	M	Dementia praecox (catatonic)	5	53	500	3
3	19	M	Dementia praecox (hebephrenic)	3	53	477	10
4	25	F	Manic-depressive psychosis	7	13	61	6
5	49	F	Involutional psychosis	10	27	203	2
6	50	F	Involutional psychosis	2	8	48	3
7	21	M	Dementia praecox (hebephrenic)	3	..	..	..
8	43	M	Organic disease of brain (tuberculosis)	..	..	..	..

TABLE 2.—*Histopathologic Changes*

Case	FD	FA	OA	Astroglia Striatum	HE + HF	Total +	Microglia (Total +)	Neurons (Total +)
1	3	4	2	2	1	12	0	0
2	3	3	2	2	3	13	3	1
3	4	5	6	2	3	20	11	7
4	2	2	1	1	3	9	4	6
5	2	2	1	1	1	7	0	1
6	6	4	4	1	3	18	0	12
7	3	1	2	1	1	8	1	3
8	3*	0	0	0	2	5	0	9

* Changes in cortical layers IV to VI only were evaluated.

collection and with cases reported in the literature shows that this progressive gliosis was not induced by the concomitant tuberculosis and was not a specific reaction of the underlying psychosis. One might expect such a pronounced proliferation of astrocytes in an arteriosclerotic brain, in old age or after a long-standing endogenous intoxication, e. g., in hepatic disease; but to find it in young persons who died of pulmonary tuberculosis without tuberculous disease of the brain itself is unusual. Yet one might hesitate to attribute the astrogliosis to the preceding injections of metrazol were it not for the striking resemblance to the histologic changes in the previously reported histopathologic studies on rabbit brains following experimental injections of metrazol.[1]

Here, too, the outstanding features were hypertrophy and hyperplasia of the astroglia, with a somewhat less pronounced progressive reaction of the microglia. If one compares, for example, figures 3 and 4 of the experimental study with figures 3 and 4 of this report, one will be impressed by the similarity of reactions in the animal and in the human brain.

The number of human brains studied is too small to permit conclusions as to the relation between the total dose of metrazol injected and the intensity of the gliosis. It seems, however, as if this reaction was less pronounced in conditions of long standing than in more recent disease of two to three years' duration (cases 3 and 6). One might think in this connection of the failure of persons with dementia praecox of long standing to react favorably to insulin or metrazol shock therapy.

The pathologic changes in the neurons were not marked, except in cases 3 and 6. The changes observed in case 6 resembled much those seen in rabbit 24, in which a total of 1,530 mg. of metrazol had been injected. However, one should remember that in these experiments the amount of metrazol injected per kilogram of body weight was from two to four times that used in case of the psychotic patients.

Four of the 6 treated patients died of tuberculosis within two to ten months after the last injection of metrazol. Like the Netherland authors, we considered the possibility that a slumbering tuberculous process might have been activated through the therapeutic procedures, since at the beginning of the treatment no evidence of tuberculosis had been found by ordinary clinical methods.

SUMMARY AND CONCLUSIONS

The brains of 6 patients with dementia praecox, manic-depressive psychosis and involutional melancholia were studied after treatment with injections of metrazol for from two to ten months.

The outstanding histopathologic features were marked hypertrophy and hyperplasia of astrocytes and, to a lesser degree, of the microglia. Disease of the ganglion cell was less pronounced, although in a case of involutional melancholia there was generalized severe disease of the neurons with neuronophagia.

Apparently in the cases of more recent illness, of from two to three years' duration, the reaction was more vigorous, with progressive glial changes, than in those of a psychosis of longer standing, of from five to ten years.

A comparison of the histopathologic changes in the human brains with previously reported observations after experimental injections of metrazol in rabbits revealed a striking similarity in the reaction of the nerve tissue in the two groups. In both instances there were marked hypertrophy and hyperplasia of the astroglia and, to a lesser degree, of the microglia, with mild disease of the neurons.

THE GUILLAIN-BARRÉ SYNDROME

POLYRADICULONEURITIS WITH ALBUMINOCYTOLOGIC DISSOCIATION

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In 1916, Guillain, Barré and Strohl [1] described a previously unrecognized type of polyneuritis characterized by definite changes in the cerebrospinal fluid. The essentials of the disease were widespread flaccid paralysis, loss of tendon reflexes, preservation of cutaneous reflexes, conservation of idiomuscular contraction on percussion, minimal changes in the electrical reactions of the muscles and nerves, occasional involvement of cranial nerves, muscle tenderness, paresthesias with little disturbance of objective sensibility and, most specifically, increase in the protein content of the cerebrospinal fluid which was not accompanied by a proportionate degree of pleocytosis. The paralysis was often of the ascending variety and of rapid onset, but recovery was also usually rapid and was complete, with no residual atrophy. The authors expressed the belief that the disease was the result of a concomitant attack on the nerve roots, peripheral nerves and muscles, probably by an infectious or toxic agent, and they termed it radiculoneuritis. They stressed the favorable prognosis, even in cases in which the paralysis was extensive and respiratory failure seemed imminent.

Numerous European observers [2] have since reported instances of this condition, referring to it as the Guillain-Barré syndrome, or as

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1. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462 (Oct. 13) 1916.

2. (*a*) Marie, P., and Chatelin, C.: Note sur un syndrome de paralysie flasque plus ou moins généralisée avec abolition des réflexes, hyperalbuminose massive et xanthochromie du liquide céphalo-rachidien, évoluant spontanément vers la guérison et de nature indéterminée, Rev. neurol. **2**:564 (Nov.-Dec.) 1916. (*b*) Draganesco, S., and Claudian, J.: Sur un cas de radiculo-névrite curable (syndrome de Guillain-Barré) apparue au cours d'une osteo-myélite du bras, ibid. **2**:517 (Nov.) 1929. (*c*) Francois; Zuccoli, G., and Montus, G.: Sur un cas de polyradiculo-névrite curable avec dissociation albumino-cytologique: Syndrome de Guillain et de Barré, ibid. **1**:95 (Jan.) 1929. (*d*) van Bogaert, L.; Philips, F.; Radermecker, J.; Radermecker, M. A., and Verschraegen, T.: Essai sur un groupe épidémique de

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"polyradiculitis with albuminocytologic dissociation and favorable outcome." Recently the condition has received interest in this country, and is being diagnosed with increasing frequency. Varieties of neuritis closely resembling those described by Guillain and Barré, but lacking certain of the essential characteristics, have also been reported and have been referred to under various terms, such as polyneuritis of unknown origin, polyradiculoneuritis, infective or febrile polyneuritis and neuronitis. It seems worth while, therefore, to review them and their relation to the Guillain-Barré syndrome and to appraise the cases in which the condition conforms most closely to the original description of Guillain and Barré in order to determine whether it constitutes a specific disease entity.

The term acute febrile polyneuritis was first used by Osler [3] in 1892. In 1917, Holmes [4] reported 12 cases of the condition and described the postmortem changes in 2. In 1918, Bradford, Bashford and Wilson [5] reported 30 cases of what they termed acute infective polyneuritis. Pathologic studies showed degenerative changes and an interstitial inflammatory reaction in the peripheral nerves and dorsal root ganglia; there were also degenerative changes in the anterior horn and Betz cells. The authors reproduced the condition in monkeys by intracerebral injections of emulsions of the spinal cord of persons who had died of the disease, and isolated a specific virus. Other observers, however, were unable to duplicate this work. Kennedy [6] and Casamajor,[7] in 1919, reported instances of myeloradiculitis occurring among troops, perhaps similar to those reported by Holmes. Kennedy used the term infective neuronitis in describing his cases, while Casamajor referred to the condition in his cases as acute ascending paralysis.

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cas de polyradiculonévrite avec dissociation albumino-cytologique du liquide céphalo-rachidien (type de Guillain et Barré), chez l'enfant et chez l'adulte, J. belge de neurol. et de psychiat. **38**:151 (March) 1938. (*e*) Biemond, A.: Quelques remarques sur l'étiologie de la maladie de Guillain-Barré, ibid. **38**:231 (March) 1938. (*f*) Roger, H., and Boudouresques, J.: Quelques réflexions sur le syndrome de Guillain-Barré, ibid. **38**:243 (April) 1938. (*g*) Riser, and Planques, M.: Les polyradiculo-névrites aiguës (Syndrome Guillain-Barré-Strohl), ibid. **38**:264 (April) 1938. (*h*) Ansay, J.: Contribution à l'étude du syndrome polyradiculo-névritique de Guillain et Barré chez l'enfant, ibid. **37**:311 (May) 1937.

3. Osler, W.: The Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, p. 777.

4. Holmes, G.: Acute Febrile Polyneuritis, Brit. M. J. **2**:37 (July 14) 1917.

5. Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88 (Oct.) 1918.

6. Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919.

7. Casamajor, L.: Acute Ascending Paralysis Among Troops, Arch. Neurol. & Psychiat. **2**:605 (Dec.) 1919.

Mettel [8] described 3 cases of acute infective polyneuritis occurring in children. These closely paralleled the cases described by Guillain and Barré, but no determinations of the protein content of the spinal fluid were made. Strauss and Rabiner [9] reported 7 cases of myeloradiculitis. There was an acute onset with involvement of the posterior nerve roots and the spinal cord, followed by rapid recovery in all cases. They expressed the belief that the disease was caused by infection of the upper respiratory tract. No determinations of the amount of protein in the spinal fluid were made. The authors stated that their cases differed from those described by Guillain and Barré because there was involvement of the spinal cord as well as of nerve roots. Barker [10] reported a case of polyradiculoneuritis in which relief followed treatment for oral sepsis. In this instance there was also involvement of the cranial nerves, and the spinal fluid contained increased amounts of protein without pleocytosis. Pinckney [11] described 5 cases of polyneuritis, in 1 of which the patient died. In all cases the spinal fluid showed increase in protein but not in cells. Two of his patients had palsy of the facial nerve, and 2 had ophthalmoplegia. He used the term acute infective polyneuritis, and expressed the belief that the increased protein content of the spinal fluid pointed to a more vigorous reaction and consequently justified a better prognosis.

Gilpin, Moersch and Kernohan [12] described a syndrome which they called neuronitis, a term first used by Mills [13] in 1898. In about half the patients studied there had been a preceding infection followed by a latent period, varying from a few days to several months, before the onset of symptoms. Motor manifestations predominated, and there was frequent involvement of cranial nerves. In 35 per cent of the patients there was weakness of the facial nerves, and 3 had papilledema. The cerebrospinal fluid in every case showed an increase in protein but not in cells. The protein content varied from 100 to 800 mg. per hundred cubic centimeters, and the cell count from 1 to 80, with an average of 12, per cubic millimeter. There were less than 24 cells in all but 3 cases.

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11. Pinckney, C.: Acute Infective Polyneuritis, Brit. M. J. **2**:333 (Aug. 15) 1936.

12. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis: A Clinical and Pathologic Study of a Special Group of Cases Frequently Referred to as Instances of Neuronitis, Arch. Neurol. & Psychiat. **35**:937 (May) 1936.

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The colloidal gold curve was of middle zone type in 50 per cent and of first zone type in 25 per cent of cases; in 25 per cent the colloidal gold test was not performed. In 4 instances the fluid was xanthochromic. The majority of the patients recovered, usually within a period varying from six months to two and one-half years. The mortality rate was 14 per cent in a series of 35 cases. Pathologic examination showed degeneration of the myelin and fragmentation of the axis-cylinders in the peripheral nerves, without evidence of inflammation. There was mild lymphocytic infiltration in the dorsal root ganglia. The authors stated the belief that the condition was caused by a filtrable virus, but they also considered the possibility of a bacteriotoxic reaction or a deficiency disease.

Juba [14] described a case of polyradiculoneuritis in which there was a history of a preceding infection. The course was rapidly fatal, and postmortem examination showed lymphocytic infiltrations, degeneration of the myelin and phagocytosis of fat. Hecht [15] reported 7 cases of acute infective polyneuritis occurring in children. The clinical course and spinal fluid findings conformed closely to those described by Guillain and Barré. In 4 of the cases there had been a recent respiratory infection, and in 1 the illness was associated with abscess of a tooth. There was frequent involvement of the facial and lower cranial nerves. Meriwether [16] reported a single case of probable neuronitis with favorable outcome. McIntyre,[17] in the same year, described a group of cases under the term infective neuronitis. Albuminocytologic dissociation was a constant finding. Death occurred in 1 case, and in this instance chromatolysis of the anterior horn cells was noted. The author classified cases of this type as follows: (1) those in which the course was mild and recovery rapid, (2) those in which there was prolonged course with death from heart failure, (3) those in which there were prolonged course and incomplete recovery and (4) those in which there was prolonged course with death from bulbar or respiratory paralysis.

Madigan and Marietta [18] reported a single case of polyradiculoneuritis with involvement of the seventh, ninth and tenth cranial nerves

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14. Juba, A.: Ueber einen perakut verlaufenen Fall von Polyneuroganglioradiculitis ascendens, Deutsche Ztschr. f. Nervenh. **142**:265, 1937; Ueber die akute aufsteigende Polyradiculoneuritis, ibid. **144**:290, 1937.

15. Hecht, M. S.: Acute Infective Polyneuritis in Childhood, J. Pediat. **11**: 743 (Dec.) 1937.

16. Meriwether, L. S.: Probable Neuronitis: Report of a Case, Proc. Staff Meet., Mayo Clin. **12**:474 (July 28) 1937.

17. McIntyre, H. D.: Infective Neuronitis, Ohio State M. J. **33**:875 (Aug.) 1937.

18. Madigan, P. A., and Marietta, S. U.: Polyradiculoneuritis, with Report of Case, Ann. Int. Med. **12**:719 (Nov.) 1938.

and an increase in protein in the spinal fluid without pleocytosis. Garvey and Slavin [19] described similar cases in which they called the condition acute infectious polyneuritis. They considered the possibility of a filtrable virus as an etiologic factor and said that they were not in accord with the statement that the high protein content of the cerebrospinal fluid indicates a good prognosis. Bassoe [20] reported 3 cases in which there were varied and multiple symptoms. He stated the belief that a single specific virus or various infective organisms might be responsible. Gillespie and Field [21] described a case occurring in a child who did not improve with the administration of vitamins or the removal of tonsils and adenoids, but showed prompt recovery after removal of all the teeth.

Another group of cases that should probably be considered with those already mentioned are those reported as instances of "acute polyneuritis with facial diplegia." Laurans,[22] in 1908, collected 18 instances of this type. In 1916, Patrick [23] discussed 29 additional cases from the literature and reported 2 of his own. Viets [24] added 2 more cases, 1 of mild course and 1 of fatal termination, in which the condition was preceded by a febrile illness. In the case of fatal outcome there was excessive protein in the cerebrospinal fluid. Taylor and McDonald [25] reported the cases of 16 patients with this syndrome. These occurred sporadically, and signs of infection were slight or absent. The febrile onset was inconstant, and there was no fixed latent period. The cerebrospinal fluid findings were presented in 6 instances. In 1 case the fluid was normal, but in the other 5 there was albuminocytologic dissociation. Of these 5, there were improvement in 3 and a chronic course in 1, and in another the patient died. Postmortem examination showed diffuse inflammation involving the neurons, with few manifestations in the spinal cord or the brain stem. The authors were unable to suggest an etiologic agent.

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19. Garvey, P. H., and Slavin, H. B.: Acute Infectious Polyneuritis, Internat. Clin. **4**:38 (Dec.) 1938.

20. Bassoe, P.: Guillain-Barré Syndrome and Related Conditions (Meningoradiculomyelitis and Meningomyeloencephalitis), Arch. Path. **26**:289 (July) 1938.

21. Gillespie, J. B., and Field, E. H.: Acute Polyneuritis of Uncertain Origin (Guillain-Barré Syndrome), J. Pediat. **14**:363 (March) 1939.

22. Laurans, A.: Des diplégies faciales au cours des polynévrites, Thesis, Paris, no. 210, 1908; cited by Taylor, E. W., and McDonald, C. A.: The Syndrome of Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **27**:79 (June) 1932.

23. Patrick, H. T.: Facial Diplegia in Multiple Neuritis, J. Nerv. & Ment. Dis. **44**:322 (Oct.) 1916.

24. Viets, H. R.: Acute Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **17**:794 (June) 1927.

25. Taylor, E. W., and McDonald, C. A.: The Syndrome of Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **27**:79 (June) 1932.

It is a question whether these syndromes, referred to under varying terms, belong to a single group of disorders. It is also a question whether the condition in cases which conformed most closely to those described by Guillain and Barré should be considered as constituting a disease entity. Cases of polyneuritis similar in many respects to those described by Guillain and Barré are being recognized with increasing frequency. It is of utmost importance to differentiate these cases if they are to be considered as representing a nosologic entity, and therefore a condition with good prognosis, from similar cases in which the outcome is less favorable. With this in mind, instances that have been observed at the University Hospital during the past four years are presented.

REPORT OF CASES

CASE 1.—R. D., a farmer aged 17 years, was admitted to the University Hospital on June 14, 1935. One week previously he had noticed weakness of the legs, which had progressed to complete paralysis and was followed by increasing weakness of the upper extremities. Three days before admission he awakened to find the right side of his face paralyzed and at the same time noticed difficulty in talking and swallowing. There had been transient paresthesia of the fingers and toes and aching pains in the arms and legs, but no marked disturbance of sensation. There was no impairment of sphincter control. No acute infection had preceded the onset of symptoms.

Examination.—The patient did not appear to be acutely ill. The temperature, pulse and respirations were normal. General physical examination showed no abnormalities. The pupils were unequal but reacted normally. There was a peripheral type of paralysis of the right side of the face. Speech was bulbar in type. There was no paralysis of the tongue or of the soft palate. The distal muscles of the upper extremities were paretic, although movements were normal at the shoulder girdles. The biceps reflexes were not obtained, and the triceps reflexes were diminished. The abdominal and cremasteric reflexes were normal. There was flaccid paralysis of the lower extremities, with bilateral foot drop. The patellar and achilles reflexes could not be obtained. Hoffmann and Babinski signs were not elicited. Tactile and superficial pain sensations were normal, but vibratory and position sensations were diminished in the lower extremities. There was marked tenderness in the muscles of both the upper and the lower extremities. Spinal fluid pressure was 100 mm. of water, and there was no block. The fluid was clear and colorless, and contained 1 mononuclear cell per cubic millimeter. The Pandy and Nonne-Apelt reactions were markedly positive, and the total protein content was 360 mg. per hundred cubic centimeters. The colloidal gold curve was 0000122210; the mastic curve was 234432, and the Kahn reaction was negative. A blood count showed no evidence of anemia or infection, and urinalysis gave normal results. Cultures of material from the throat were sterile for diphtheria bacilli.

Course.—The patient was given conservative treatment, with a high vitamin diet, strychnine sulfate, 0.001 Gm. three times a day, and physical therapy in the form of massage and contrast baths. The day after admission he was able to move his feet, and the following day he could perform weak movements with the entire right lower extremity. There was progressive improvement in the use

of both upper and lower extremities and of the facial muscles. The patient was able to sit up in a chair at the end of a month and could walk in six weeks. He was discharged seven weeks after admission, at which time there were no residuals.

CASE 2.—K. T., a boy aged 9, who was admitted on Aug. 22, 1936, one week previously had noticed aching pains in the calves, followed in three days by progressive weakness of the legs and unsteadiness in walking. Two weeks before the onset of these symptoms the patient had had a brief illness characterized by fever and earache, but with no discharge from the ears.

Examination.—The patient was well developed but poorly nourished; he walked with an ataxic gait and showed generalized weakness of the lower extremities. There were no manifestations of involvement of the cranial nerves aside from hyperemia of the optic disks. There was marked fatigability of the upper extremities, but no definite muscular weakness. The biceps and triceps reflexes were diminished; the abdominal reflexes were weak. There was flaccid paresis of both lower extremities without atrophy, and the patellar and achilles reflexes were absent. There was a markedly positive Lasègue sign, and the Kernig and Brudzinski signs were weakly obtained. There were exquisite tenderness in the muscle masses of the forearms, upper portion of the arms, thighs and legs and in the achilles tendons, and cutaneous hyperesthesia over the posterior aspect of both calves. Proprioceptive sensations were normal. Electrical tests showed no reaction of degeneration. Spinal puncture on August 22 showed the fluid to be under increased pressure, but the patient was straining at the time; there was no block. There were 8 cells per cubic millimeter; the Kahn reaction was negative; the colloidal gold curve was 1111000000; the mastic curve was 110000, and the total protein content was 125 mg. per hundred cubic centimeters. On October 23 the pressure was normal; there were 5 cells per cubic millimeter; the reaction for globulin was still positive, but the colloidal gold and mastic curves showed no reduction and the protein content was 35 mg. per hundred cubic centimeters.

Course.—The patient was given 250 cc. of citrated adult blood at the time of admission, since a diagnosis of poliomyelitis was considered; he was then treated with massage, contrast baths and increasing passive and active exercise. He was given a vitamin B_1 concentrate by mouth. There was progressive improvement in the use of the lower extremities, and he was able to walk without assistance in one month. Hospitalization was prolonged by the development of slowly resolving pneumonia, but he was without symptoms at the time of discharge, on Nov. 13, 1936.

CASE 3.—C. DeV., a laborer aged 28, who was admitted on Jan. 15, 1938, one month previously had noticed sharp pains in the left arm and hand and aching pain in the calves, after which there developed numbness in the fingers and toes, which ascended to involve both arms and legs. A few days later rapidly progressing paralysis of the lower extremities appeared and was followed by paresis of the upper extremities. There had been no disturbance of the bowels or bladder, and there was no history of preceding infection.

Examination.—The patient did not appear to be acutely ill. The temperature, pulse and respirations were normal. There were no abnormalities of the cranial nerves. There was marked weakness of the upper extremities, with a decrease in muscle tone. The biceps reflexes were not obtained, and the triceps reflex was present only on the left. The abdominal reflexes were present. There was flaccid paresis of the lower extremities. The patient walked with a steppage gait and showed marked ataxia. Patellar and achilles reflexes were absent. There was no Hoffmann or Babinski sign. Sensory examination showed patchy and inconstant

areas of hypalgesia and hypesthesia in both upper and lower extremities, more marked in the distal portions. Vibratory sensation was diminished at the ankles. Muscle tenderness was increased in the calves. Spinal fluid pressure was 110 mm. of water with no block. The fluid was clear and colorless and contained 1 lymphocyte per cubic millimeter. The Pandy and Nonne-Apelt reactions were positive, and the total protein was 160 mg. per hundred cubic centimeters. The Kahn reaction was negative; the colloidal gold curve was 0012220000, and the mastic curve was 332210. Urinalysis gave normal results, and the blood count failed to show evidence of anemia or infection.

Course.—The patient was given a high vitamin diet, massage and contrast and whirlpool baths. There was progressive improvement, and he was able to walk without difficulty at the time of discharge, three weeks after admission. He returned to work one month later, and has noticed no further manifestations.

CASE 4.—E. S., a boy aged 14, who was admitted to the University Hospital on Dec. 31, 1938, three weeks previously had noticed weakness of the calf muscles while running, and a week later soreness in the calves. Three or four days before admission he had noticed numbness of the fingers and toes, followed by generalized weakness of the upper and lower extremities, which progressed rapidly. There was no history of recent infection.

Examination.—The patient was well developed. The temperature, pulse and respirations were normal. There were no abnormalities of the cranial nerves. There were loss of abduction at the shoulders, weakness of flexion and extension at the elbows, marked paresis of the muscles of the forearms and hands and a "claw" deformity of the fourth and fifth fingers of the left hand, with atrophy of the thenar and hypothenar eminences. The muscles of the back and abdomen were weak, and the patient was unable to sit up without support. There was flaccid paresis of the lower extremities, with marked weakness in all movements. Aside from involvement of the left hand, no atrophy was noted, and there were no fibrillations. The tendon reflexes were all absent, and the abdominal reflexes were hypoactive. There were Kernig and Lasègue signs bilaterally. Muscle tenderness was present in both the upper and the lower extremities. Vibratory sense was impaired in the wrists and ankles, and position sense was diminished in the fingers and toes. Cutaneous sensations were reduced over the distal portions of the extremities and were absent in the distribution of the left ulnar nerve. A spinal puncture on Jan. 4, 1939 showed no block. The fluid was xanthochromic and contained 8 cells per cubic millimeter. The Kahn reaction was negative; the colloidal gold curve was 0001110000; the mastic curve was 222100, and the total protein was 268 mg. per hundred cubic centimeters. On Februray 6 the spinal fluid pressure was 140 mm. of water. The fluid was still slightly xanthochromic and contained 6 cells per cubic millimeter. The Pandy and Nonne-Apelt reactions were positive; the Kahn reaction was negative; the colloidal gold curve was 0000110000; the mastic curve was 444321, and the total protein was 286 mg. per hundred cubic centimeters. Examinations of the blood and urine gave normal results.

Course.—The patient was given large doses of a vitamin B concentrate by mouth; for two weeks there was no change in his condition. There was then gradual improvement, with decrease in tenderness and some return of muscle power, followed by more rapid improvement and disappearance of the clawhand and the bilateral foot drop. Three weeks after admission he was given gentle massage and contrast baths, and two weeks later he was able to be up for short periods. When discharged at the end of two months he was completely recovered.

CASE 5.—K. I., a salesman aged 25, who was admitted to the University Hospital on Feb. 22, 1939, three weeks previously had had an acute infection of the upper respiratory tract and a week later had noticed aching pains and some weakness of the lower extremities, with numbness and tingling of the hands and feet. A week before admission he had had a chill, followed by headache, pain in the back, nausea and vomiting, and shortly after this there developed increased pain and progressive weakness of both the upper and the lower extremities. Within twenty-four hours he was unable to move the arms or the legs. There was constipation, requiring enemas for relief.

Examination.—The patient was well developed and appeared to be acutely ill. The temperature was 98.6 F., and the pulse and respiratory rates were 112 and 20 per minute, respectively. The throat was reddened and injected, and there were many coarse rales throughout both lungs. The patient was conscious and alert. There was flaccid paresis of the upper and lower extremities, especially marked in the latter. There was no atrophy, and no fibrillations were observed. The optic nerves were hyperemic, with early papilledema. There was paresis of the muscles of facial expression bilaterally, more marked on the right, with some weakness of the muscles of mastication on each side. There was no weakness of the soft palate or of the tongue. The biceps, triceps, patellar and achilles reflexes were absent; the abdominal reflexes were not obtained, and the cremasteric reflexes were weak. There was no response to plantar stimulation. Kernig and Brudzinski signs were positive bilaterally. Sensory examination showed diminished superficial pain, temperature and tactile sensations in the distribution of the lower two branches of the fifth nerve bilaterally. Cutaneous, vibratory and position senses were lost in the distal portions of the lower extremities and diminished in the proximal portions and in the upper extremities. Sensations were perceived normally over the thorax and abdomen. There was marked tenderness over the nerve trunks in both the upper and the lower extremities. The patient was incontinent of both urine and feces.

Examination of the blood and urine gave normal results, and the Kahn reaction was negative. Spinal puncture on February 25 showed a pressure of 160 mm. of water, with no block. The fluid was xanthochromic but clear; there were 33 cells per cubic millimeter, all of which were lymphocytes. The Pandy and Nonne-Apelt reactions were positive; the Kahn reaction was negative; the colloidal gold curve was 0001110000; the mastic curve was 343210, and the total protein was 268 mg. per hundred cubic centimeters. On March 16 the spinal fluid pressure was 85 mm. of water; the fluid was clear and colorless, and there were 4 cells per cubic millimeter. The Pandy reaction was still positive; the Nonne-Apelt reaction was negative; the colloidal gold curve was 0012110000; the mastic curve was 210000, and the total protein was 100 mg. per hundred cubic centimeters.

Course.—The patient was given no medication, but was placed on a high vitamin, high caloric diet. Two days after admission the pain became less marked, and he noticed a return of sensation and motor power. The incontinence persisted for several days but was gone at the end of the first week. Within two weeks the muscle tenderness had left, and there was a marked return of muscle power. At this time physical therapy, in the form of massage and under water exercise, was started, with still more rapid improvement as a result. At the time of discharge, four weeks after admission, the patient was able to walk for short distances and showed no residual foot drop; he had good use of the upper extremities, and the facial weakness and papilledema had disappeared.

CASE 6.—E. M. D., a housewife aged 45, who was admitted on March 7, 1939, one month previously had had an infection of the upper respiratory tract, which was diagnosed as influenza, and two weeks after this had noticed subcostal pain and numbness of the fingers and toes. This was followed by pain and weakness of the legs and later of the upper extremities, which progressed until she was unable to walk or use her arms. She had been confined to bed during the week before admission. There was a history of constipation and urinary retention.

Examination.—The patient was somewhat confused and irrational at the time of admission. The temperature, pulse and respirations were normal. The throat was injected, and the tongue was red and furrowed. Coarse rales were heard throughout both lungs. The cranial nerves were normal, except for bilateral weakness of the muscles supplied by the seventh nerve. The extremities were hypotonic, and there was marked weakness of the legs, with some weakness of the arms. The patient was unable to sit up without assistance. There was atrophy of the small muscles of the hands, but no fibrillations were observed. The biceps and triceps reflexes were diminished, and the patellar and achilles reflexes were absent. The abdominal reflexes were not obtained. The Hoffmann and Babinski signs were absent. Superficial, vibratory and position sensations were diminished in the lower extremities, with more marked change in the distal portions, and there was moderate disturbance of all types of sensation in the upper extremities. There was exquisite tenderness over the muscle masses and nerve trunks. There was a positive Lasègue sign bilaterally, and Kernig and Brudzinski signs were suggested.

Examination of the blood and urine gave normal results, and the Kahn reaction of the blood was negative. Spinal puncture on March 10 revealed a pressure of 70 mm. of water, with no block. The fluid was clear and colorless; there were 6 lymphocytes per cubic millimeter; the Kahn reaction was negative; the Pandy and Nonne-Apelt reactions were strongly positive; the colloidal gold curve was 0001211000; the mastic curve was 233210, and the total protein was 412 mg. per hundred cubic centimeters. On March 28 the findings were similar, except for a total protein content of 210 mg. On May 9 the amount of protein was decreased to 76 mg. per hundred cubic centimeters. Determination of the total protein content of the blood serum on March 21 gave 7.2 Gm. per hundred cubic centimeters, with 4.2 Gm. of globulin, 3 Gm. of albumin and an albumin-globulin ratio of 0.7.

Course.—The patient was given a high vitamin, high caloric diet and in addition thiamine hydrochloride, nicotinic acid, ascorbic acid and liver extract. There was no change for two weeks, when the pain began to diminish gradually. The patient required codeine for the relief of pain for about three weeks. After one month there was more rapid change, with disappearance of the muscle tenderness and return of motor power. Physical therapy was started, and two months after admission the patient was able to walk with assistance. At the time of discharge, one month later, the pain, tenderness and sensory changes had disappeared, and there was complete return of muscle power.

CASE 7.—J. N. S., a schoolboy aged 15, who was admitted on April 15, 1939, four weeks previously had had a mild infection of the upper respiratory tract, followed within a few days by numbness and tingling of the fingers and toes and then of the arms and legs. A week later he noticed pain and muscle tenderness in the upper and lower extremities, followed by rapidly progressing weakness and disability. He had also noted constipation and urgency and frequency of urination, with occasional incontinence.

Examination.—The patient was well developed and well nourished, and was alert and cooperative. The temperature, pulse and respirations were normal. There

were no abnormalities of the cranial nerves. There was flaccid paresis of the upper and lower extremities with bilateral wrist drop, most marked on the left, and bilateral foot drop. No muscular atrophy or fibrillations were noted. The biceps and triceps reflexes were diminished; the abdominal reflexes were sluggish, and the patellar and achilles reflexes were absent. There was no Hoffmann or Babinski sign. Cutaneous sensations were diminished over the upper and lower extremities, with the more pronounced changes in the distal portions. Vibratory sensation was diminished at the ankles, and position sense was impaired in the fingers and toes. There was marked tenderness over the muscle masses and the nerve trunks. A spinal puncture on April 21 showed the spinal fluid pressure to be 120 mm. of water, with no block; the fluid was xanthochromic but clear, and contained 1 cell per cubic millimeter. The Kahn reaction was negative; the Pandy and Nonne-Apelt reactions were positive; the colloidal gold curve was 0001110000; the mastic curve was 333210, and the total protein was 333 mg. per hundred cubic centimeters. On May 5 the fluid was clear and colorless, and contained 4 cells per cubic millimeter. The reaction for globulin was still positive; the gold curve was 0012210000; the mastic curve was 331000, and the total protein was 200 mg. per hundred cubic centimeters. On June 1 the colloidal gold and mastic curves were flat, and the total protein was 160 mg. per hundred cubic centimeters. The Kahn reaction of the blood was negative and routine examinations of the blood and urine gave normal results throughout the period of hospitalization.

Course.—The patient was treated with a high vitamin, high caloric diet, and was given thiamine hydrochloride by mouth. He noticed marked anorexia, and there was little change in his condition during the first two weeks. After this, however, the muscle tenderness began to disappear gradually, the sensory changes became less marked and there was beginning return of motor power. The improvement became more rapid, and it was soon possible to institute massage, under water exercises and, later, passive and active exercise. The pain and tenderness disappeared about one month after admission, and two weeks later he was able to be up for short periods. At the time of discharge, June 17, 1939, the patient showed complete recovery, with no residual sensory changes or motor weakness.

The clinical picture in the 7 preceding cases conforms closely to that originally described by Guillain and Barré. In each case there was a sudden onset of symptoms. A slight infection preceded the onset in 4 instances. Motor disturbances were more marked than was sensory involvement. There was little evidence of atrophy or of change in the electrical reactions. The tendon reflexes were absent, but the cutaneous reflexes often remained normal. Involvement of the facial nerves was noted in 3 cases and hyperemia or edema of the optic disks in 2. There were some sphincter involvement in 3 instances and evidences of meningeal irritation in 4. In all cases there was definite albuminocytologic dissociation. The total protein content of the fluid in the acute stage varied between 125 and 412 mg., with an average of 214 mg. per hundred cubic centimeters. The cell count varied between 1 and 33, with an average of 6, per cubic millimeter. The cerebrospinal fluid was xanthochromic in 3 cases. In all instances there were changes in the colloidal gold curve. The patients were young, the average age being 22 years. Six of 7 were males. The outcome was favorable, complete recovery without residuals taking place in an average of eight weeks.

TABLE 1.—*Cases in which There Was Complete Recovery*

Case No.	Age, Years	Sex	Duration of Disease at Admission	Total Duration of Illness	History of Preceding Infection	Involvement of Cranial Nerves	Sphincter Involvement	Meningeal Signs	Cerebrospinal Fluid			
									Color	Cell Count, per Cu. Mm.	Total Protein, Mg. per 100 Cc.	Colloidal Gold Curve
1	17	M	1 week	2 months	None	Right facial nerve; bulbar speech	None	None	Colorless	1	360	0000122210
2	9	M	1 week	5 weeks	Yes	Hyperemia of optic disks	None	Kernig and Brudzinski	Colorless	8	125	1111000000
									Colorless	5	35	0000000000
3	28	M	1 month	7 weeks	None	None	None	None	Colorless	1	160	0012220000
4	14	M	4 days	2 months	None	None	None	Kernig	Xanthochromic	8	268	0001110000
									Xanthochromic	6	286	0000110000
5	25	M	2 weeks	6 weeks	Yes	Papilledema; facial nerve bilaterally	Incontinence of bowel and bladder	Kernig and Brudzinski	Xanthochromic	33	268	0001110000
									Colorless	4	100	0012110000
6	45	F	2 weeks	10 weeks	Yes	Facial nerve bilaterally	Retention; constipation	Kernig and Brudzinski	Colorless	6	412	0001211000
									Colorless	5	210	0001210000
									Colorless	5	76	0001100000
7	15	M	4 weeks	10 weeks	Yes	None	Incontinence; constipation	None	Xanthochromic	1	333	0001110000
									Colorless	4	200	0012210000
									Colorless	2	160	0000000000

The disease in the following 6 cases, in 5 of which the patients were males, presented a clinical picture similar to that in the foregoing group, but had a more prolonged or chronic course.

CASE 8.—F. T., a molder aged 45, who was admitted on Nov. 2, 1934, six months previously had noticed pain and numbness in the hands and arms and later in the feet and legs. This had progressed gradually, and with it there had developed weakness of all four extremities and later atrophy of the small muscles of the hands and forearms, with bilateral foot drop. The patient noted frequency of urination and nocturia, but no incontinence. He had lost 30 pounds (13.6 Kg.) in weight in six months.

Examination.—The patient was undernourished and appeared to be chronically ill. The blood pressure was 170 systolic and 100 diastolic. The ankles were edematous. The teeth were carious, with marked pyorrheic absorption. There were no abnormalities of the cranial nerves. There was flaccid paresis of the upper and lower extremities, with atrophy of the small muscles of the hands and forearms, clawing of the hands and foot drop bilaterally. The biceps and triceps reflexes were present, being slightly more active on the right; the abdominal reflexes were active; the patellar reflexes were diminished, especially on the right, and the achilles reflex was absent bilaterally. There were hypesthesia and hypalgesia over the area of distribution of the right ulnar nerve. Vibratory and position senses were diminished in the lower extremities. There was marked tenderness in the calf muscles and the achilles tendon on both sides. The Kahn test of the blood, the blood count and urinalysis gave normal results, and examination of the hair, skin and nails for arsenic and mercury gave negative reactions. A spinal puncture on November 5 showed a pressure of 100 mm. of water, with no block. The fluid was clear and colorless; there were 5 cells per cubic millimeter; the Pandy and Nonne-Apelt reactions were positive; the Kahn reaction was negative; the colloidal gold curve was 0013310000; the mastic curve was 332100, and the total protein was 104 mg. per hundred cubic centimeters. On Feb. 20, 1935, there were 14 cells per cubic millimeter; the colloidal gold curve was 0001100000; the mastic curve was 110000; the total protein was 86 mg. per hundred cubic centimeters, and the results of the other tests were unchanged.

Course.—The patient was given high vitamin diet and physical therapy in the form of bakes and whirlpool baths, with some improvement in the muscle tenderness but little change in strength. He was discharged after seven weeks, his condition showing no essential change. He was again hospitalized from Feb. 11 to March 18, 1935, at which time there was slight return of strength in the hands, but no diminution in atrophy and no change in the foot drop. When he was finally discharged, four months after his first admission and ten mnoths after the onset of symptoms, there was no appreciable change in his condition.

CASE 9.—M. C., a farmer aged 47, who was admitted on May 28, 1936, two weeks previously had noticed numbness of the fingers and toes, which gradually ascended to involve both arms and legs. Associated with this there was progressive weakness of the extremities, which continued to complete paralysis. There were some pain and muscle tenderness, especially in the calves. The patient had noticed ease of fatigue and some puffiness of the eyelids during the three years before the onset of symptoms.

Examination.—The temperature, pulse and respirations were normal. The blood pressure was 155 systolic and 90 diastolic. There was flaccid paresis of all four extremities, with bilateral wrist and foot drop. The biceps and triceps reflexes

were weakly obtained; the knee and achilles jerks were not elicited. The abdominal reflexes were absent. There was no Hoffmann or Babinski sign. No atrophy or fibrillations were noted. Vibration, motion and position sensations were diminished in the hands and feet. There were hypesthesia and hypalgesia in all four extremities, more marked distally than proximally. Muscle tenderness was acute. The spinal fluid pressure was 180 mm. of water, with no block. There were no cells. The Pandy and Nonne-Apelt reactions were positive; the Kahn reaction was negative; the colloidal gold curve was 0001100000; the mastic curve was 000000, and the total protein was 93 mg. per hundred cubic centimeters. The urine gave a 2 plus reaction for albumin, but there were no red blood cells and the urea clearance test gave normal results. There was no anemia. Agglutination tests for organisms of the typhoid or Brucella group gave negative results, as did examination of the hair, skin and nails for arsenic or mercury.

Course.—The patient was given a high vitamin diet with supplementary vitamin feedings. He was treated also with massage and under water exercises. There was gradual decrease in the muscle tenderness without much change in the muscle power; at the time of discharge, one month after admission, the patient was able to move his toes but had had no other return of function. When last heard from, on April 17, 1939, three years after the onset of his symptoms, there had been some further improvement, but he still had bilateral foot drop and a very weak grip, and there was residual atrophy of the small muscles of the hands and feet. He had been unable to return to work.

CASE 10.—L. E. O., a nurse aged 24, who was admitted on Sept. 15, 1937, six weeks previously had had fever accompanied by headache, backache and sore throat; a diagnosis of pharyngitis was made. Shortly afterward, however, she began to notice stiffness of the neck, pain in the muscles of the back and marked nausea and vomiting. A week later shooting pains developed in the arms and legs, and weakness was noted in the left leg and in the right foot, followed by clumsiness and difficulty in using the left arm and hand. There were marked abdominal distention and some difficulty with urination.

Examination.—The patient was extremely nervous and restless, but was conscious and alert. There were no abnormalities of the cranial nerves. The temperature, pulse and respirations were normal. She was unable to walk or stand, and there was flaccid paresis of both lower extremities and the left arm. There was marked weakness of the dorsiflexors of both feet and of the hamstring muscles on the left. No atrophy or fibrillations were observed. The tendon reflexes were overactive in the upper extremities; the abdominal reflexes were weakly obtained; the patellar reflexes were diminished, especially on the left, and the left achilles reflex was absent while the right was weak. There was no Hoffmann or Babinski sign. There was marked muscular tenderness, especially in the muscle masses in the posterior regions of the thighs and in the calves. Vibratory and position sensations were normal, as were all superficial sensations. The Kahn test of the blood, the blood count, and the routine examination of the urine gave normal results. Spinal puncture showed a pressure of 80 mm. of water, with no block. There was no increase in cells. The Kahn reaction was negative; the Pandy and Nonne-Apelt reactions were positive; the colloidal gold curve was 0001210000; the mastic curve was 112100, and the total protein was 174 mg. per hundred cubic centimeters.

Course.—The patient was extremely restless and apprehensive, and complained of a great deal of pain at the time of admission. She entered the hospital only for diagnosis and was discharged at the end of a week, before active therapy

could be started. She was advised to take large amounts of vitamin B. Two months after discharge she was able to be up on crutches and one month later could walk a little with assistance. Nine months after the onset of the symptoms she still had foot drop on the left and difficulty in using the left hand, and twenty-one months after the onset still walked with a limp, could not use the left hand for skilled work and had atrophy of the muscles of the left foot and leg.

CASE 11.—F. A. W., a farmer aged 54, who was admitted on April 15, 1938, eight days previously had awakened to find his hands and feet numb. Within the next three days the numbness ascended to the elbows and hips, and with this change there developed marked weakness of all four extremities. There were shooting and burning pains, which were worse at night. There was no history of disturbance of the bowels or bladder.

Examination.—The patient did not appear to be acutely ill. The temperature, pulse and respirations were normal. There were no abnormalities of the cranial nerves. There was flaccid paresis of all four extremities, most marked in the distal portions. There was no atrophy, and no fibrillations were observed. The biceps, triceps, patellar and achilles reflexes were absent, but the abdominal and cremasteric reflexes were preserved. There was no Hoffmann or Babinski sign. There was a positive Lasègue sign bilaterally. Tactile and superficial pain sensations were diminished in the extremities, more marked distally than proximally, and vibratory sense was diminished at the ankles. Position sense was intact. There was marked tenderness in all muscle masses and in the achilles tendons. Examination of the urine and blood and the Kahn test of the blood gave normal results. The spinal fluid pressure was 150 mm. of water, with no block. There were 21 lymphocytes per cubic millimeter. The Pandy reaction was positive; the Nonne-Apelt and Kahn reactions were negative; the colloidal gold curve was 0000110000; the mastic curve was 122210, and the total protein was 143 mg. per hundred cubic centimeters. Agglutination tests gave negative results for organisms of the typhoid and Brucella groups.

Course.—The patient was given a high caloric, high vitamin diet and a concentrated preparation of vitamin B_1; in addition he was treated with massage and active and passive exercise. There was improvement in the pain and muscle tenderness, but only slight change in muscle power. About a week after admission there developed a febrile illness of unknown origin, which lasted for about ten days. When discharged, two months after admission, the patient was able to feed himself, but had contractures of the hands with atrophy of the thenar and hypothenar and interosseous muscles. There had been no improvement in the feet. The patient was last seen on July 20, 1938, three and a half months after the onset of symptoms; at that time there was still marked atrophy with deformity of the hands, and the patient was still unable to move his feet or legs.

CASE 12.—G. H. F., a farmer aged 27, who was admitted to the University Hospital on Aug. 22, 1938, in the previous March had first noticed soreness and stiffness in the muscles of the thighs and later in the calves. After this there developed numbness and weakness of the legs and thighs, and later numbness and weakness of the upper extremities. There were shooting pains in the arms and legs. The patient had been confined to bed for four months prior to the time of admission. There was no history of disturbance of the bowels or bladder.

Examination.—The patient was undernourished and showed evidence of marked loss of weight. The temperature, pulse and respirations were normal. The cranial nerves were not involved. There was flaccid paralysis of the arms and

legs. The patient was able to move the fingers slightly, but could not move the arms at the elbows or the shoulders and was unable to make any movement with the lower extremities. The tendon and abdominal reflexes were absent. Superficial pain and tactile sensations were diminished in the arms and legs, more marked distally than proximally, and vibratory and position senses were absent in the hands and feet. There was acute tenderness in the muscle masses and in the tendons. The Kahn test of the blood, blood count and urinalysis gave normal results. The spinal fluid pressure was 120 mm. of water, with no block. The fluid was xanthochromic, and there were 7 cells per cubic millimeter. The Pandy and Nonne-Apelt reactions were positive; the Kahn reaction was negative; the colloidal gold curve was 0000011110; the mastic curve was 223443, and the total protein content was 880 mg. per hundred cubic centimeters.

Course.—The patient had pneumonia shortly after his admission to the hospital and was acutely ill for three weeks. He improved from this and was treated with a high vitamin diet and physical therapy in the form of massage and passive and active exercise. There was slow improvement. The tenderness and sensory changes became less marked, but there was little change in motor power. At the time of discharge, three months after admission, there had been but slight return of function. The patient was able to feed himself without assistance, but was unable to walk. When last seen on April 26, 1939, thirteen months after the onset of symptoms, there was still weakness of all movements, with deformities due to atrophy of the small muscles of the hands and paralysis of the dorsiflexors of the feet and toes. The biceps, triceps and patellar reflexes were weakly present, but the achilles reflexes were absent. There were no abnormalities of sensation.

CASE 13.—S. T., a shipping clerk aged 43, who was admitted to the University Hospital on April 18, 1939, six weeks before had noticed numbness and tingling of the great toe bilaterally; this had ascended to involve the feet and the legs. Two weeks later he noted numbness of the fingers and then of the arms and hands, followed by progressive weakness of the upper and lower extremities, with difficulty in using the hands for skilled actions and bilateral foot drop. There was no history of disturbance of the bowels or bladder.

Examination.—The patient was well developed and did not appear to be acutely ill. The temperature, pulse and respirations were normal. There were no abnormalities of the cranial nerves. There was flaccid paresis of the upper and lower extremities, with weakness of the fingers and hands, atrophy of the interosseous and thenar muscles and bilateral foot drop. The biceps reflexes were active; the triceps reflexes were diminished, and the patellar and achilles reflexes were absent. The abdominal reflexes were diminished on the right and absent on the left. There was no Hoffmann or Babinski sign. There was diminished superficial sensation over the distal portions of the extremities. Vibratory and position sensations were absent in the feet and ankles and diminished in the fingers and hands. There was increased tenderness in the muscle masses and the achilles tendons. The Kahn test of the blood, the blood count and urinalysis gave normal results. Spinal puncture on April 19 showed a pressure of 140 mm. of water, with no block; the fluid was clear and colorless, and there were 2 cells per cubic millimeter. The Kahn reaction was negative; the Pandy and Nonne-Apelt reactions were positive; the colloidal gold curve was 0001100000; the mastic curve was 221000, and the total protein was 133 mg. per hundred cubic centimeters. On May 24 all the reactions were similar, and the total protein was 160 mg. per hundred cubic centimeters.

Course.—The patient was given a high vitamin diet plus thiamine hydrochloride; in addition, massage and passive and active exercise were prescribed. There was rapid improvement in the tenderness, but very slow change in the muscular weakness. At the time of discharge, on June 24, he was able to move his fingers and toes, but was unable to walk or to feed himself. When last seen, on Sept. 21, 1939, seven and a half months after the onset, the patient was able to feed and dress himself, but still had atrophy and disability of the hands and feet and was able to walk only with a cane.

The clinical and laboratory findings in this group are similar to those in the first. The average values for the total protein content, 230 mg. per hundred cubic centimeters, and for the cell count, 7 cells per cubic millimeter, correspond with those in the first, although in all but 1 case in this group the total protein content was lower and in 2 cases the cell count was definitely increased. The fluid was xanthochromic in 1 case. It is noteworthy that in none of these cases was there involvement of the cranial nerves. In 2 instances there was minimal involvement of the bladder, and in 1 signs slightly suggestive of meningeal irritation were noted. The onset in most of the cases was more gradual and the involvement was less frequently symmetric than in the first group. In only 1 case was there a history of preceding infection. The majority of the patients in this group were older than those in the first, the average age being 40. There was residual atrophy with deformities in every instance.

Still another group of cases that must be considered in a survey of the syndrome of polyradiculoneuritis with albuminocytologic dissociation are those in which the outcome is fatal. The following 2 belong to this group.

Case 14.—H. M., a bricklayer aged 52, who was admitted to the University Hospital on Sept. 23, 1936, three weeks previously had noticed that his feet felt clumsy and heavy; ten days later there developed numbness and weakness of the toes and feet, which progressed rapidly to complete paralysis. Three days before admission the patient noted numbness and disability in the arms and hands, and after this had difficulty in breathing. There had been no pain and no disturbance of the bowels or bladder. No illness of any type had preceded the onset of the symptoms, but the patient had had two abscessed teeth extracted a month before.

Examination.—The temperature, pulse and respirations were normal at the time of admission. There were no palsies of the cranial nerves, but the patient's voice was hoarse and he was unable to speak above a whisper. He could not move his arms at the shoulders or elbows, but was able to grip weakly, especially with the right hand. He was unable to make any movement with the lower extremities. The biceps, triceps, abdominal, patellar and achilles reflexes were absent. There was no Hoffmann or Babinski sign. There was no muscular atrophy, and no fibrillations were seen. Tactile and superficial pain sensations were diminished in the arms and legs, the changes being more pronounced in the distal portion of the extremities. Position sense was absent in the ankles and toes but was retained in the fingers. There was increased tenderness in the muscle masses and the

achilles tendons. Vibratory sense was absent at the ankles and diminished at the wrists. There was a Lasègue sign bilaterally. The Kahn test of the blood, the blood count and urinalysis gave normal results. Agglutination tests gave negative reactions for organisms of the typhoid or Brucella groups. The spinal fluid pressure was 160 mm. of water, with no block. The fluid was clear and colorless and contained 6 cells per cubic millimeter. The Pandy and Nonne-Apelt reactions were strongly positive; the Kahn reaction was negative; the amount of dextrose was normal. The colloidal gold curve was 0111222110; the mastic curve was 234443, and the total protein was 229 mg. per hundred cubic centimeters. Cultures of the spinal fluid were reported as sterile.

Course.—The weakness of the upper extremities became more marked, and dyspnea, dysarthria and dysphagia developed. The respirations became rapid and shallow and the pulse weak. Signs of pneumonia developed, and the patient died one week after admission.

Autopsy.—Postmortem examination showed acute purulent bronchitis and bronchopneumonia. There were edema of the brain and congestion of the spinal cord, most pronounced in the area of the anterior horns. The motor nuclei in the anterior horns showed varying types of degenerative change—shrinking and pyknosis in some and accumulation of fat in others, with occasional swollen and vacuolated cells. There were no inflammatory changes either in the spinal cord or in the nerve roots. There was no demyelination. The nuclei of the medulla showed changes similar to those in the anterior horns.

CASE 15.—Mrs. B. S., a woman aged 48, who was admitted on Oct. 10, 1938, two weeks before had suffered from an attack of respiratory difficulty diagnosed as asthma, which was relieved by oral and hypodermic medications. A week after this she noticed heaviness and progressive weakness of the feet, which ascended to involve the legs and later the arms and hands. Paresthesias were present in the hands and feet, but there was no definite loss of sensation. There had been no disturbance of the bowels or bladder.

Examination.—The patient was dyspneic and moderately cyanotic at the time of admission. Moist rales were heard throughout both lungs, and there was an area of dulness which corresponded to the base of the left lung. There was no disturbance of superficial sensation or of the sense of position; vibratory sense was diminished at the ankles, and deep pain sense was increased in the calf muscles and the achilles tendons. There was slight but definite weakness of the muscles supplied by the left facial nerve. Aside from shrugging the shoulders, the patient was unable to carry out any movement of the upper or lower extremities. There was no atrophy, and no fibrillations were seen. All tendon and cutaneous reflexes were absent. There was no Hoffmann or Babinski sign. Urinalysis, the blood count and the Kahn test of the blood gave normal results. The spinal fluid pressure was 150 mm. of water and there was no block. There was 1 cell per cubic millimeter; the Pandy and Nonne-Apelt reactions were strongly positive; the Kahn reaction was negative; the colloidal gold curve was 0011100000; the mastic curve was 122100, and the total protein was 111 mg. per hundred cubic centimeters. Examination of the urine, hair and nails for lead and arsenic gave negative results.

Course.—The paralysis of the extremities persisted. Two days after admission there developed difficulty in swallowing and talking, which progressed to complete bulbar palsy, accompanied by marked respiratory distress. Pneumonia developed, and the patient died two weeks after admission.

Autopsy.—Postmortem examination showed bronchopneumonia in the lower lobe of the left lung, with atelectasis in the lower lobe of the right. Gross examination of the brain revealed pronounced hyperemia. In the spinal cord the predominant congestion was in the anterior horns, the cells of which showed marked swelling with displacement of the nuclei. The tigroid substance was broken down; in some cells it was evenly distributed throughout and dustlike, while other cells stained deep pinkish blue with thionine and showed no details. Many of the swollen cells contained large vacuoles, some three or more, which gave them a honeycombed appearance. Scarlet red and Marchi stains showed accumulations of lipoids within the neurons. The vessels of the cord were congested and engorged, but there was no evidence of infiltration, exudation or degeneration of the myelin sheaths. The motor nuclei within the medulla showed changes similar to those in the anterior horn cells. There was no inflammatory reaction in the ganglia and no definite evidence of any pathologic process in the peripheral nerves.

In both the preceding cases the clinical picture was similar to that in the first two groups, but resulted in death. Clinically, these cases may be considered as instances of acute ascending paralysis of the Landry type, and case 15 has been reported as such.[26]

TABLE 2.—*Cases in Which the Course Was Chronic*

Case No.	Age, Yr.; Sex	Duration of Disease at Admission	Total Duration of Illness	History of Preceding Infection	Cerebrospinal Fluid				Comment
					Color	Cell Count, per Cu. Mm.	Total Protein, Mg. per 100 Cc.	Colloidal Gold Curve	
8	45 M	6 months	10 months; no change	None	Colorless Colorless	5 14	104 86	0013310000 0001100000	Frequency; nocturia
9	47 M	2 weeks	3 years; no change	None	Colorless	0	93	0001100000	
10	24 F	5 weeks	21 months; residuals	Yes	Colorless	0	174	0001210000	Difficulty in urination
11	54 M	8 days	3½ months; residuals	None	Colorless	21	143	0000110000	Lasègue sign
12	27 M	5 months	13 months; residuals	None	Xanthochromic	7	880	0000011110	
13	43 M	6 weeks	7½ months; residuals	None	Colorless	2	133	0001100000	

COMMENT

The 15 cases reported are instances of polyneuritis with albuminocytologic dissociation. In all of them the involvement was predominantly motor, with extensive flaccid paralysis, often of ascending type and usually symmetric. There was significant atrophy only in cases of the chronic form. Sensory changes were present, but were more marked subjectively than objectively. The tendon reflexes were involved to a greater extent than the cutaneous. Electrical reactions and muscle response to percussion were preserved, or even exaggerated. In most

26. De Jong, R. N.: Acute Ascending Paralysis, with Clinical and Pathologic Report on Cases with Fatal Termination, J. A. M. A., to be published.

cases the involvement was manifest particularly in the distal portions of the extremities, although some authors have stressed the proximal involvement. Manifestations of disturbances of the cranial nerves, involvement of the sphincters and meningeal signs were noted in some cases. The outstanding observation, present in every case, was the marked increase in the protein content of the cerebrospinal fluid without a proportionate increase in cells. In some cases the protein rose progressively during the onset of the disease and remained high during convalescence. This hyperalbuminosis was accompanied by an early or middle zone change in the colloidal gold curve, and in some cases by xanthochromia. Merritt and Fremont-Smith [27] reported that such changes in the cerebrospinal fluid are rare in the various polyneuritides but do occur in association with the condition which they classified as "polyneuritis of unknown etiology," especially in the instances of polyneuritis accompanied by facial diplegia. They stated that the hyperalbuminosis may be due to involvement of the roots or of the nerve sheaths where they come in contact with the subarachnoid space, or to an alteration in the permeability of the choroid plexus for protein. Some authors, Pinckney,[11] for example, expressed the belief that the xanthochromia and increased protein content point to a more vigorous meningeal reaction and therefore to a better prognosis. Garvey and Slavin,[19] however, asserted that the increased protein is an evidence of involvement of the nerve roots and is in no way related to the prognosis. Collier [28] stated that both cells and protein show little or no increase in neuritides due to exotoxins, moderate increase in association with extrinsic poisons, such as alcohol and arsenic, and most marked increase in the neuritides of unknown origin. The increase in both cells and protein, he concluded, is present as a challenge to invasion of the tissues; their presence in a high degree has good prognostic significance, and their absence suggests either that the pathologic process is uncombated and overwhelming or that it is of little virulence and demands no particular effort of local reaction.

The etiologic factor in the cases here reported and in the related cases described in the literature has not been definitely determined. In some instances the symptoms were preceded by a slight infection or associated with a focus of infection, and as a consequence an infectious, toxic or bacteriotoxic origin has been suggested.[29] None of our patients

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27. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1937, pp. 180-185.

28. Collier, J.: Peripheral Neuritis, Edinburgh M. J. **39**:601 (Oct.) 1932.

29. (*a*) Heernu: Origine toxique de la paralysie dans le syndrome de Guillain-Barré, J. belge de neurol. et de psychiat. **39**:250 (April) 1939. (*b*) Laruelle, L., and Massion-Verniory, L.: Contribution au syndrome polyradiculonévritique de Guillain-Barré, ibid. **37**:635 (Oct.) 1937. (*c*) van Bogaert and others.[2d] (*d*) Ansay.[2h]

gave a history of exposure to a known toxin, and none had fever of consequence or leukocytosis associated with the onset of the neurologic symptoms. A vitamin deficiency has been considered as the etiologic factor, for it is known that many varieties of polyneuritis, formerly believed to be of toxic origin, are associated with deficiency of a specific vitamin. Vitamins were used in the treatment of most of our patients, but their efficacy could not be determined. Ayer [30] has recently stated that during the last decade there has been a tendency to attribute all neuritides to a deficiency of vitamin B_1, but unfortunately therapy along this line has given variable and often unsatisfactory results. It may be that there are multiple causes, as stated by Hecht [15] and by Laruelle and Massion-Verniory,[29b] with various toxic or infectious factors in individual cases. This theory is borne out by the fact that the condition rarely occurs in epidemic or pandemic forms. Strauss and Rabiner,[9] however, reported 7 cases, all occurring in the spring of 1926, and considered the possibility of an epidemic. Van Bogaert and his co-workers [2d] also reported a group of cases under the name "epidemic polyradiculoneuritis." Most observers today believe that the etiologic factor is a specific filtrable virus having a special affinity for the peripheral nerves, nerve roots and ganglia, and probably related to the viruses of poliomyelitis and encephalitis.[31] Cobb and Coggeshall [32] classified acute febrile polyneuritis, acute infective polyneuritis, encephalomyelitis and Landry's paralysis as virus infections. The Matheson Commission,[33] in its third report, suggested that the Guillain-Barré syndrome may be a virus disease allied to epidemic encephalitis, and myeloradiculoneuritic forms of lethargic encephalitis, similar in many respects to the present cases, have been described by Bassoe; [34] Barker, Cross and Irwin,[35] and

30. Ayer, J. B.: Report on Medical Progress: Neurology, New England J. Med. **221**:105 (July 20) 1939.

31. Alajouanine, T.; Thurel, R.; Hornet, T., and Boudin, G.: La polyradiculonévrite aiguë généralisée avec diplégie faciale et paralysie terminale des muscles respiratoires et avec dissociation albumino-cytologique, Rev. neurol. **1**:681 (March) 1936. Barker.[10] Biemond.[2e] Garvey and Slavin.[19] Roger and Boudouresques.[2f]

32. Cobb, S., and Coggeshall, H. C.: Neuritis, J. A. M. A. **103**:1608 (Nov. 24) 1934.

33. The Guillain-Barré Syndrome, in Report of the Matheson Commission: Epidemic Encephalitis: Etiology, Epidemiology, Treatment, New York, Columbia University Press, 1939, pp. 44-47.

34. Bassoe, P.: The Delirious and Meningoradicular Types of Epidemic Encephalitis, J. A. M. A. **74**:1009 (April 10) 1920.

35. Barker, L. F.; Cross, E. S., and Irwin, S. V.: On the Epidemic Acute and Subacute Non-Suppurative Inflammations of the Nervous System Prevalent in the United States in 1918-1919: Encephalitis; Encephalomyelitis; Polyneuritis; and Meningo-Encephalo-Myelo-Neuritis, Am. J. M. Sc. **159**:157 (Feb.) 1920.

Bériel and Devic.[36] Guillain [37] stated the belief, however, that polyradiculoneuritis should not be considered a peripheral form of epidemic encephalitis. He stated that the syndrome bearing his name is caused by a related, but specific, neurotropic virus. Barré [38] asserted that the disease is associated with a filtrable virus or an organism not yet isolated. The Matheson Commission concluded that the Guillain-Barré syndrome is generally assumed to be caused by a filtrable virus, although the possibility of a toxic or infectious process or an adventitious circumstance is still to be considered.

The pathologic observations have been variously described, and there have been no consistent reports. In the cases described by Guillain and Barré the patients recovered, and consequently the pathologic changes are not known. Taylor and McDonald [25] described a diffuse inflammatory reaction about the neurons, with minimal involvement of the spinal cord and brain stem. Hecht [15] mentioned changes in the nerve roots and peripheral nerves, with occasional lesions in the meninges, anterior horn cells and even the cortex. De Ajuriaguerra [39] described, in cases of experimental polyneuritis similar in many respects to those we have reported, lesions in the peripheral nerves, the muscles or the spinal cord, stating that the changes might be either central or peripheral, usually, however, involving the two portions simultaneously. Gilpin, Moersch and Kernohan [12] observed no evidence of inflammation; changes described by them were purely degenerative and were most marked in the peripheral nerves, although there was slight involvement of the spinal cord, especially in the anterior horns. The predominant change was edema, with patchy degeneration of the myelin and fragmentation of the axis-cylinders in the peripheral nerves. Balduzzi [40] and Longo [41] both observed congestion of the spinal roots, with many small, diffuse hemorrhages causing hemorrhagic radiculitis. Dechaume [42] concluded that

36. Bériel, L., and Devic, A.: Les formes "périphériques" de l'encéphalite epidémique, Presse méd. **33**:1441, 1925.

37. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936; Synthèse de la discussion, J. belge de neurol. et de psychiat. **38**:322 (April) 1938.

38. Barré, J. A.: Considérations diverses sur le syndrome de polyradiculonévrite avec dissociation albumino-cytologique, J. belge de neurol. et de psychiat. **38**:313 (April) 1938.

39. de Ajuriaguerra, J.: Les polynévrites expérimentales, Rev. neurol. **2**:433 (Nov.) 1938.

40. Balduzzi, O.: Anatomia patologica della "Polyradiculitis acute curabilis" con dissociazione albuminocitologica: Sindrome di Guillain-Barré, Riv. di pat. nerv. **51**:288, 1938.

41. Longo, V.: Sulla polinevrite acuta febbrile: Studio clinico e istologico, Riv. di pat. nerv. **51**:313, 1939.

42. Dechaume, J.: Polynévrite infectieuse ou schwannite à virus neurotrope (Documents histo-pathologiques), Rev. neurol. **1**:403 (March) 1932.

the predominant pathologic change was in the sheath of Schwann, and noted an increase in the number and volume of the sheath cells, diffuse lymphocytic infiltration of the nerve roots and peripheral nerves and some degeneration of the myelin. He termed the condition "schwannitis," due to a virus having a special affinity for the schwannophilic cells. Barker,[10] Alajouanine and his associates,[31] de Morsier and Steinmann,[43] and Garvey and Slavin [19] and others have suggested the same pathology and etiology. In conclusion, it may be stated that there is as yet no general agreement regarding the pathologic changes underlying the condition in these cases, especially since in many in which postmortem examination has been made the picture has not conformed too closely to the descriptions of Guillain and others. In general, however, the pathologic observations have consisted of degenerative changes, involving principally the nerve roots and the peripheral nerves, with some secondary degeneration in the anterior horn cells.[44] There is no definite evidence of an inflammatory reaction in the nerves, nerve roots, meninges or anterior horn cells, no glial proliferation or cellular infiltration and no degeneration of the myelin sheaths within the spinal cord.

The differential diagnosis is of paramount importance. The sudden onset of flaccid paralysis, accompanied by muscle tenderness and at times by signs of meningeal irritation, may suggest poliomyelitis. This is especially true in cases occurring in children. The diagnosis of polyneuritis can usually be made, however, on the basis of the minimal febrile reaction, the presence of some sensory changes and the symmetry of the motor involvement, and is confirmed by spinal fluid examination. If there is any doubt, it is better to consider a diagnosis of poliomyelitis until disproved and to institute contagious precautions and specific therapy, as was done in case 2. The various types of neuritis can usually be differentiated. The clinical course and spinal findings in the more common toxic neuritides, such as those due to lead and arsenic, and in the deficiency neuritides usually make the diagnosis definite. In postdiphtheritic polyneuritis, on the other hand, there is often hyperalbuminosis, so that a careful history, and at times bacteriologic studies, may be necessary. There may also be an increase in the protein content of the spinal fluid in cases of syphilitic polyneuritis, of far advanced polyneuritis accompanying pregnancy and of plumbism in which the involvement is radicular rather than neuritic. In fact, every variety of polyneuritis, whether it is of toxic, infectious or metabolic origin, may be accompanied by increase in the spinal fluid protein if the process

43. de Morsier, G., and Steinmann, J.: Les polyradiculonévrites: forme aiguë curable; forme à évolution fatale, Presse méd. **44**:1890 (Nov. 21) 1936.

44. Accornero, F.: Zur Frage der Rückenmarksveränderungen bei Polyneuritis, Deutsche Ztschr. f. Nervenh. **143**:137, 1937.

is extensive enough to involve the nerve roots and the spinal cord as well as the peripheral nerves. The condition must be distinguished from polioencephalomyelitis and from the forms of epidemic encephalitis in which the involvement is primarily peripheral. Finally, the cases in this group must be differentiated from instances of acute ascending paralysis of the Landry type. Here the differentiation may be extremely difficult early in the course of the disease, and in cases of fatal termination it may be impossible. Many authors have expressed the belief that Landry's paralysis is a rapidly progressing form of polyneuritis of unknown origin.[28] It is generally believed today, however, that acute ascending paralysis is a disease entity, at least as far as mode of onset and progression of symptoms are concerned, even though the etiologic factors may differ in individual cases.[45]

As the etiology of polyradiculoneuritis with albuminocytologic dissociation is not known, specific treatment cannot be suggested. Guillain [37] advised antiseptic measures, such as intravenous injections of salicylates and intravenous and intramuscular administration of quinine, methenamine and colloidal silver. He also suggested electrotherapy in the form of ionization of iodine or calcium. Barker [10] and Gillespie and Field [21] advocated removal of focal infections. Strauss and Rabiner [9] advised treatment by intravenous injection of typhoid vaccine and other methods of inducing artificial fever. Various therapeutic measures were used in our cases. Vitamins, especially concentrates of vitamin B_1 and B_2, were administered empirically, but their effectiveness is not known, particularly since some of the patients showed signs of improvement very soon after admission to the hospital. As the condition in many instances seems to be self limited, we have stressed the use of palliative measures plus physical therapy as soon as it can be carried out, in order to preserve muscle tone and prevent the development of deformities. Contrast and whirlpool baths are used early in the illness, with massage as soon as the muscle tenderness disappears, followed by passive and assisted active exercise. Conditions indistinguishable from poliomyelitis at the outset should be treated as such until a definite diagnosis can be made.

The cases reported here can obviously be divided into three groups: (1) those in which the duration is short and the prognosis favorable; (2) those in which the course is prolonged or chronic, and (3) those in which the termination is fatal. This classification differs in some respects from that of McIntyre,[17] already mentioned, and that of de Morsier and Steinmann,[43] who listed two forms, one from which the patient recovers and one which results in death due to involvement of

45. Gordinier, H. C.: Poliomyelitis Versus Landry's Paralysis, Ann. Int. Med. 3:892 (March) 1930. De Jong.[26]

the respiratory nerves. They stated that at the outset the two varieties cannot be differentiated. The cases in our first group corresponded closely with those described by Guillain, Barré and Strohl,[1] and with those reported by other European observers as cases of the Guillain-Barré syndrome.[2] The question has been raised whether the chronic and fatal forms should be placed in the same category and whether the syndrome as a whole should be interpreted to include them. The cases in the second group were differentiated from those in the first by the slightly more prolonged onset and by the development of atrophy, contractures and persistent residuals. The fatal cases could not be differentiated at the outset, but bulbar and diaphragmatic involvement occurred early and was associated with respiratory failure. The predominant clinical manifestations, the early signs and symptoms and the cerebrospinal fluid changes were so similar in the cases of all three groups that it would seem justifiable to consider all three types as members of the same general disease group unless more conclusive information regarding the etiologic agent and the nature of the pathologic changes should alter this contention.

Guillain and others asserted that the syndrome bearing his name was a specific clinical and nosologic entity, distinct from other forms of polyneuritis. They included, however, only those cases in which complete recovery resulted. On the basis of our observations, cases of the chronic and fatal varieties in many instances cannot be differentiated, especially early in the course of the disease, from those in which the outcome will be favorable. Therefore, if the Guillain-Barré syndrome is to be considered a disease entity the term must not be restricted to cases in which recovery results, but should be used to designate all cases of polyradiculoneuritis with albuminocytologic dissociation. Thus, the original viewpoints of Guillain and Barré must be broadened to include also the cases of chronic and fatal course, and the prognosis must be guarded at the outset of the illness, until the clinical course can be more specifically appraised.

Case Reports

NEUROPSYCHIATRIC COMPLICATIONS FOLLOWING SEVERE LOSS OF BLOOD

NORMAN REIDER, M.D., TOPEKA, KAN.

While the neuropsychiatric complications of the primary anemias are well known clinically, there are, at least in the American literature, no references to the neurologic complications which come from acute anemia due to hemorrhage. Interest in this subject was stimulated a few years ago, when, during observations in a case to be reported in this paper, in which aphasic and apraxic complications occurred after a severe hemorrhage, the idea was conceived that perhaps the neurologic sequelae of acute hemorrhage are not so rare as their absence from the American literature would lead one to believe. It was, however, not only because of the unusualness of the case but also because of the problem of the existence of the syndrome as a clinical entity that this study was made.

The history of the subject is a long one. Hippocrates made the observation that "delirium and convulsions arising out of severe loss of blood have a poor prognosis." Celsius is said to have remarked that "bleeding either kills or cures." Avicenna denied this, stating: "There are those who believe that strength depends on the abundance of blood and weakness on its absence, but this is not so." Centuries later this controversy continued in the arguments between phlebotomists and anti-phlebotomists in regard to the effects of bloodletting. The same tenor of discussion, in a sense, even finds its way to present day literature, as shown by the conclusions presented by Durand [1] less than a year ago, in which he warned against the dangers of venesection. That acute loss of blood could produce neuropsychiatric sequelae had been observed now and then throughout the nineteenth century, but no one before Worms,[2] in 1931, had made a comprehensive and systematic study of the subject.

The clinical syndromes and the precipitating factors that have been described are numerous. The syndrome has been said to be precipitated by venesection, hemoptysis, hematemesis, uterine and rectal bleeding, epistaxis, postoperative anemia and hemorrhage following lacerations and gunshot wounds. The most frequently encountered neurologic sequel is hemiplegia, occurring not only in older persons with arteriosclerosis or hypertension, in which lowering of the blood pressure apparently leads within several hours to ictus and hemiplegia, but also in younger

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Read before the Chicago Neurological Society, Jan. 18, 1940.

1. Durand, P.: Pourquoi le rôle de la saignée peut-il être néfaste, au cours sous la menace d'un ictus, chez un hypertendu? Presse méd. **47**:1072 (July 5) 1939.

2. Worms, R.: Les accidents nerveux consécutifs aux pertes de sang, Paris, Gaston Doin & Cie, 1931.

patients with no evidence of vascular disease. The hemiplegia may be merely transitory, lasting only a few days. In some cases death occurs, as in that reported by Bouveret,[3] the case of a woman aged 40 in whom aphasia and then hemiplegia developed after hemoptysis; only cerebral edema was observed at autopsy. Worms presented a similar case, that of a man aged 58, in which the brain showed no softening or hemorrhage and the cerebral vessels were without disease. Occasionally hemiplegia does not arise until 36 hours after the bleeding, as in a case reported by Barbier and Wenger.[4] Worms also reported a case of monoplegia following acute hemorrhage. In some of these cases there was prompt recovery from the hemiplegia immediately after transfusion.

That signs of involvement of the pyramidal tracts may occur without the loss of motor function was shown by Worms in his report of 4 cases, in 2 of which the pathologic signs disappeared after transfusion.

Complications involving the spinal cord are rare. Roger and Olmer [5] reported 2 cases of mild involvement of the cord, in 1 of which, that of a woman aged 45 with severe secondary anemia caused by bleeding hemorrhoids, there was loss of deep sensibility in the lower extremities, and in the other, the case of a woman aged 41 suffering from severe uterine hemorrhages, there was involvement of the posterolateral region of the cord. Both patients recovered under therapy. Involvement of the cord may be severe, as in the cases of Martin,[6] Landry [7] and McConnell,[8] in which paraplegia occurred after extensive loss of blood. In Martin's cases the condition was due to severe uterine and rectal bleeding. In McConnell's case, in which the severe anemia was secondary, pronounced gastric hemorrhage was followed by immediate loss of vision and the development of optic atrophy, and several days later by progressive weakness in the legs, with a picture of disease of the posterolateral region of the cord; the signs of injury to the cord disappeared with improvement of the anemia, but the optic atrophy persisted. Landry's case is of particular interest, since each severe epistaxis was followed by a recurrence of the paraplegia; there was slow regression of the signs until the next epistaxis. Thompson [9] reported a case of subacute combined degeneration of the cord associated with bleeding from a gastric ulcer.

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3. Bouveret, L.: Aphasie; hémiplégie; apoplexie; suite d'hémorragie gastrique; autopsie, Rev. de méd., Paris **19**:81-87, 1899.

4. Barbier and Wenger: Hémiplégie au cours d'une anémie aiguë post-hémorragique, Lyon méd. **151**:261-269 (Feb. 26) 1933.

5. Roger, H., and Olmer, J.: Troubles nerveux au cours d'anémies post-hémorragiques, Sang **10**:357-362, 1936.

6. Martin, M., cited by Worms.[2]

7. Landry, J., cited by Worms.[2]

8. McConnell, J. W.: Spinal Cord Changes Following a Secondary General Anemia with Recovery, J. Nerv. & Ment. Dis. **34**:658, 1907.

9. Thompson, T.: A Case of Subacute Combined Degeneration of the Spinal Cord, Brain **34**:510, 1911-1912.

The rarest complication is apparently polyneuritis, of which there exists the record of only 1 case, reported by Duhot,[10] occurring in a woman aged 24 with a rupture complicating tubal pregnancy.

Convulsions may also occur. Binswanger[11] reported the case of a woman aged 26 who had severe uterine bleeding after an abortion. She became disoriented and lethargic and had jacksonian convulsions on the right side, followed by right flaccid hemiplegia without aphasia. She recovered in a month. The same author also reported 2 similar cases, but the condition in those cases was complicated by vascular disease, which was not present in the first case.

Involvement of cranial nerves has also been observed; by far the most common sequel is amaurosis due to involvement of the optic nerves and the development of primary optic atrophy. Many such cases have been reported by Worms, Langeron[12] and Fuchs;[13] the last-mentioned author especially emphasized the therapeutic value of immediate transfusion. Worms reported a case of posthemorrhagic hemianopia. There are also cases of involvement of motor nerves of the eyes and of the trigeminal, facial and auditory nerves.

The importance of loss of blood in the production of mental symptoms was stressed by both Pinel and Esquirol. Worms[14] cited other cases in which postoperative psychoses were definitely related to the production of severe anemia from loss of blood. An example, especially instructive, was that of a hemophilic boy aged 14 who, after the removal of nasal growths, suffered severe loss of blood which led to a confusional state with auditory hallucinations. The red blood cell count at this time was 1,200,000; a transfusion of 250 cc. of blood restored the patient immediately to a normal psychic state. The boy was not in shock during the time of the psychosis.

In the cases of the aforementioned syndromes in which postmortem study was made, no focal lesions such as hemorrhage or thrombosis to account for the focal signs were revealed. Likewise, even in cases in which amaurosis occurred study of the optic tracts and nerves revealed no pathologic change. The latter statement is difficult to accept, but the fact is so reported by Langeron, who studied 4 cases. In general, the pathologic studies made leave much to be desired.

There has been relatively little work on laboratory animals that sheds much light on the mechanism of the production of the neurologic syndromes. The most pertinent of all the experiments is that reported by Worms,[14] who discussed in general the difficulty of producing

10. Duhot, R.: Contribution à l'étude des névrites par ischémie (nerf optique et nerfs périphérique), Thesis, Lille, no. 7, 1913.

11. Binswanger, O.: Corticomotorische Reiz- und Erschöpfungssymptome auf dem Boden einer Hirnanämie, Deutsche med. Wchnschr. **42**:1530, 1916.

12. Langeron, L.: (*a*) A propos des accidents nerveux post-hémorragiques, Lyon méd. **152**:176-177 (Aug. 13) 1933; (*b*) Accidents nerveux post-hemorragiques, J. de méd. et chir. prat. **106**:201-206 (March 25) 1935.

13. Fuchs, A.: Zur Therapie der Sehstörung nach schwerem Blutverlust, Wien. med. Wchnschr. **78**:1426 (Nov. 3) 1928.

14. Worms, R.: A propos de quelques troubles nerveux consécutifs aux pertes de sang; le rôle des hémorragies dans la pathogénie des accidents de la ligature carotidienne, J. de chir. **41**:215-228 (Feb.) 1933.

hemiplegia in laboratory animals by ligation of the carotid artery. He was successful, however, in producing hemiplegia in the following way: The right carotid artery in rabbits was tied, and 20 cc. of blood was removed without any effect. Twenty days later the removal of 25 cc. of blood caused left hemiparesis. Worms commented that rabbits normally withstand the ligation well, but when a relatively severe loss of blood is added, hemiplegia is provoked. This experiment is of particular interest as being in line with the recent study by Poppen,[15] who commented on the necessity of conservation of blood or maintenance of a proper blood pressure level in patients on whom ligation of the anterior cerebral artery is done.

REPORT OF CASE

History.—A healthy veterinarian, aged 41 at the time of the onset of the illness, was gored by a bull in August 1933 and sustained a severe laceration of the rectum and perineum and a fracture of the left femur. He did not suffer shock or loss of consciousness. After the injury he was taken to a small country hospital, where the perineal lacerations were sutured. The next day he had an open reduction of the fracture of the femur, with a good initial result.

Two weeks later, while lying quietly in bed and apparently convalescing well, he had a sudden severe hemorrhage from the perineum. His life was despaired of for twenty-four hours, and stimulative treatment, but no transfusion, was given. A bleeding vessel in the perineum was found and ligated. Several hours after the onset of the hemorrhage there developed what appeared from the description to be complete motor aphasia. The patient improved slowly, and as he began to recover he noted that the right hand was weak. Irregularities in heart beat were also noted at this time, but these disappeared with the continuation of rest. After a few weeks speech began to return, and thereafter he had minimal difficulty in expressing himself. He continued to complain, however, of weakness in the right hand. Still another effect of the severe hemorrhage was noted in the delay of union of the fracture. After a series of operations, it was not until May 1935 that the femur began to show slight signs of union. He was then able to walk with the aid of a brace.

The patient continued to complain of weakness in the right hand, which kept him from writing and doing odd jobs around the house. He did not note any difficulty with the right leg or sensory symptoms or signs at any time.

Examination.—I first examined the patient in June 1937, almost four years after the original injury. The outstanding and most important finding was that power in the right hand was excellent, much better than that in the left, and that the difficulties were due not at all to weakness but to apraxia and dysgraphia. There was also a distinct tremor of the right hand. The biceps and pectoral reflexes on the right were a little more active than those on the left. No signs of involvement of the pyramidal tracts were present. Two point discrimination and stereognostic sense were intact. Speech was normal except for slight hesitation in expression at times. Psychiatric examination disclosed a slight defect in immediate retention and mild euphoria. At this time, to hasten union of the fracture, which was still not completely healed, the orthopedic surgeon instituted

15. Poppen, J. L.: Ligation of the Left Anterior Cerebral Artery: Its Hazards and Means of Avoidance of Its Complications, Arch. Neurol. & Psychiat. **41**:495-503 (March) 1939.

treatment by means of mecholyl iontophoresis. Fifteen of these treatments were given the patient, and the clinical impression was gained that they aided his recovery, for after several years of a practically stationary physical and neurologic condition, improvement came about rapidly in six months. In December 1937 the patient was able to discard the brace because good union in the fracture had been obtained. Meanwhile, marked neurologic improvement also occurred. The apraxia had almost completely disappeared and the dysgraphia was much less marked. The tremor was still present. Six months later the patient was able to resume work and now is almost completely recovered. At the last examination he still had a little tremor and slight hesitation in speech, but the handwriting was good and there was no incapacitation due to weakness of the hand. He was able to handle a knife skilfully in his work. He showed no evidence of defect in memory or of emotional instability.

COMMENT

Perhaps prior consideration in discussion should be given to whether there actually exists such a syndrome as a neurologic complication of acute hemorrhage. Opposed to the establishment of such a syndrome is, of course, the principle of parsimony. It would certainly be more accurate to explain the neurologic complications, if at all possible, on the basis of the preexisting pathologic process which produced the hemorrhage rather than on the grounds of the hemorrhage itself. However, a review of the cases shows that this desirable logical explanation is not satisfactory in accounting for the findings. For instance, in a consideration of the case that has just been reported, the question may reasonably arise whether the neurologic complications could not have resulted from a fat embolus or an embolus produced during the transient period of cardiac irregularity. Such possibilities of the complicated origin of the sequelae exist in all the cases reviewed. But the overwhelming weight of evidence in favor of the existence of the syndrome as such is based on the fact that in all of these cases there was the common factor of severe loss of blood, followed within a relatively consistent period by a neurologic complication. A second important consideration is the clinical fact of the disappearance of serious signs following a transfusion.

Another point worthy of notice concerns the mechanism by which such sequelae are produced. Undoubtedly the acute anemia and anoxia in themselves are potent factors by virtue of the temporary devitalization of organs and the consequent production of immediate functional, if not organic, change. Nevertheless, this is not sufficient explanation for the apparent selectivity demonstrated in many cases. Why are only the pyramidal tracts affected in some persons and only the cord or optic nerves in others? Consideration of this question must revive the old concept of the locus of least resistance. In the case just reported, this concept fits well in the clinical picture, for it is known that centers having control over skilled acts develop last and are probably most vulnerable.

On the basis of the foregoing observations, one more speculative note may be introduced. It seems possible that whether the actual damage is in a single area or in multiple areas its production must be mediated through the vascular system and, at least in some cases, there is sufficient evidence to warrant the assumption that the lesion was

due to overcompensatory vasoconstriction in response to the hemorrhage. This assumption gains support from the transitory and reversible nature of some of the complications observed clinically, and a little additional support, admittedly not altogether convincing, from the absence of definite pathologic lesions observed post mortem.

Other theories in regard to the mechanisms of the production of the syndrome were discussed by Worms in an effort to explain the observed facts. He attempted to show that some damage to the liver must be present in these cases before the syndrome can be produced, but this contention is not borne out by his own case reports. The contention of others that the syndrome is produced only in persons with general debility who suffer severe hemorrhage is, furthermore, contradicted by the appearance of the syndrome in persons who are apparently healthy except for the factor causing severe hemorrhage. Many questions can be raised which are impossible to answer with present knowledge, especially the one as to why so many persons can withstand rather large loss of blood without any harmful effects. It may be pointed out that reports in the literature of cases in which adequate studies on the blood have been made show that in the presence of vascular disease, hypertension or a debilitating disease only a moderate hemorrhage is necessary to provoke neurologic complications, but in healthy persons the hemorrhage apparently must be severe, with at least a great enough loss of blood to lower the red cell count to 2,000,000 or less.

SUMMARY

A review of the literature and a description of a case in which aphasic and apraxic complications followed a severe hemorrhage lead to the consideration that it is justifiable to speak of the syndrome of neurologic sequelae of acute severe hemorrhage. A discussion of the diverse manifestations of the syndrome is presented, as well as a consideration of the possible means of production. It is not at all unlikely that no single explanation will account for the syndrome in every case. Of practical importance is the recognition that the syndrome exists and that immediate transfusion often causes the disappearance of the neurologic signs.

DISCUSSION

Dr. Benjamin Boshes, Chicago: Is not the important factor the drop in blood pressure, particularly the diastolic, rather than the anemia per se? A number of years ago I observed and reported a case in which about every ten minutes there was a drop in blood pressure—50 or 60 mm. of mercury systolic and from 20 to 30 mm. diastolic. With each fall in pressure the patient experienced hemiplegia and motor aphasia. I explained the cerebral symptoms as due to loss of peripheral resistance, so that as the latter fell the blood was not forced out to the cortex. Several years ago, Dr. Spiller reported a similar case in the transactions of the Philadelphia Neurological Society and supported this concept. A blood transfusion does not raise the red cell count markedly, but it decreases the shock and raises the peripheral resistance, thus providing blood to the cortex. Hence the neurologic defects disappear.

Dr. Norman Reider, Chicago: There are reports in the literature of similar instances of neurologic complications from long-standing orthostatic hypotension. I cannot believe there was not a great element of shock, but those who reported

these cases denied in many instances that shock existed. There is shock in some cases without doubt, but the protocols I have studied have not shown a sufficient drop in diastolic pressure in some instances, for example, in a case of hypertension with vascular disease in which the blood pressure on venesection dropped from 210 systolic and 120 diastolic to 170 systolic and 90 diastolic. I think that that is not sufficient to produce shock; yet the syndrome occurred. I am sure that the drop in blood pressure is sufficient to account for the syndrome in some cases but does not account for it in all cases or explain the problem of selectivity. From a study of all the cases, I have concluded that there are possibly anatomic factors to explain the selectivity. Except for the ophthalmic symptoms in some instances the neurologic complications in almost all cases in which there was bleeding from rectal or uterine disease were restricted to the cord. When bleeding has been from other sources there is much more likelihood of the complication being cerebral.

DIFFUSE TUBERCULOSIS OF THE PITUITARY GLAND SIMULATING TUMOR, WITH POSTOPERATIVE RECOVERY

C. C. Coleman, M.D., Richmond, Va., and J. M. Meredith, M.D., Charlottesville, Va.

The occurrence of diffuse tuberculosis of the pituitary gland as an isolated surgical lesion simulating tumor is practically unknown. Furthermore, when its removal is followed by apparent cure, together with relief of the associated severe headache and serious visual impairment, a report of the case in considerable detail appears not only justified but desirable.

REPORT OF CASE

Bitemporal headache and visual failure of twelve months' duration. Primary optic atrophy and enlargement of sella turcica. Incomplete bitemporal hemianopia; vision in left eye reduced to counting fingers. Large intrasellar mass disclosed at operation; diagnosed histologically as diffuse, noncaseous tuberculosis of pituitary gland. Satisfactory primary recovery with complete relief of headache and entire restoration of visual fields and visual acuity to normal, continuing three and one-half years after operation (to date).

History.—Mrs. Laura Q., a housewife aged 57, white, was referred by Dr. E. G. Gill and Dr. J. Lawson Cabaniss, of Roanoke, Va., and was admitted to the neurosurgical service of the Memorial Hospital, Richmond, Va., on June 1, 1936, complaining of visual failure and bitemporal headache. She had been in fairly good health until June 1935, when she first noticed bilateral impairment of vision, which progressed to near blindness in the left eye. Vision improved at intervals, but two weeks before admission it became worse than it had been at any previous time; the patient was greatly worried concerning the possibility of blindness. Several months before admission bitemporal headache had developed and had continued steadily until hospitalization.

The familial and the past history were unimportant except for the fact that the patient had fallen as a child and had sustained a depressed fracture of the cranial vault, apparently without disabling sequelae.

Examination.—The temperature was 98 F., the pulse rate 60 per minute and the respiratory rate 20 per minute. The blood pressure was 110 systolic and 80 diastolic. The patient was well developed and obese; she was alert and cooperative, although she complained of considerable headache. A slightly depressed cranial fracture of long standing could be palpated in the left parietal region. The heart and lungs appeared normal. Physical examination otherwise gave normal results.

Neurologic examination showed that the sense of smell was normal on each side. There was marked bilateral primary optic atrophy. Vision was greatly

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reduced in the left eye; incomplete bitemporal hemianopia was present (fig. 1), although only the upper nasal quadrant remained in the left visual field. The other cranial nerves were normal. The patient was right handed. There was no aphasia, astereognosis or relative weakness of any extremity. The biceps and triceps jerks were equal bilaterally, but the knee and ankle jerks could not be elicited on either side. Ankle clonus and the Hoffmann and Babinski signs were absent. Reactions to all tests for cerebellar function, including those of station and gait, were satisfactory.

Urinalysis gave normal results except for a very slight trace of albumin and from 25 to 30 leukocytes per high power field (voided specimen). A complete blood count was also normal except for a white cell count of 4,800 per cubic millimeter. The Wassermann and the Kahn reaction of the blood were negative. The basal metabolic rate (June 4, 1936) was —12 per cent. The fasting level of the

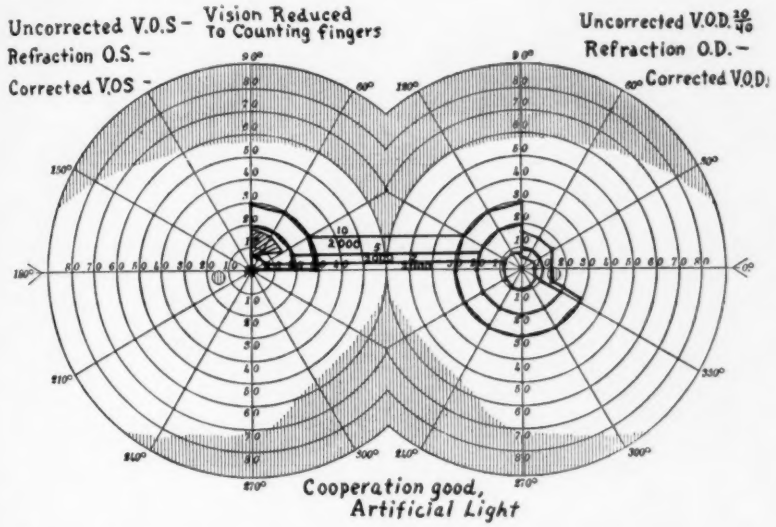

Fig. 1.—Preoperative visual fields (June 1, 1936, nine days before operation). Vision in the left eye is confined entirely to the upper nasal quadrant, and an incomplete temporal defect is present in the right eye. Vision in the left eye is reduced to counting fingers only.

blood sugar was 84 mg. per hundred cubic centimeters; nonprotein nitrogen content was 28 mg. per hundred cubic centimeters. Roentgen examination of the skull on June 2, 1936, by Dr. F. B. Mandeville, showed the sella to be 25 mm. in length and 15 mm. in depth (normal measurements, 12 by 10 mm.). There was marked thinning of the posterior clinoid processes and of the floor of the sella; the sella was "ballooned," an intrasellar mass thus being demonstrated.

Because of the patient's age, the possibility of carcinoma of the pituitary body or a metastatic lesion of some type was considered preoperatively, in addition to the more probable diagnosis of pituitary adenoma.

Operation.—On June 10, with the patient under anesthesia induced by avertin with amylene hydrate and procaine, one of us (C. C. C.) performed a left transfrontal craniotomy; the dura was opened transversely 3 or 4 cm. above the

sphenoid ridge. After tapping of the anterior horn of the left lateral ventricle, the left frontal lobe was retracted upward and backward. The left olfactory nerve was first visualized and then the left optic nerve; the latter nerve was white, flat and ribbon-like. Below and between it and the right optic nerve was a large, bulging, circumscribed mass with a peculiar, smooth, brownish capsule. The left internal carotid artery was seen immediately lateral to the left optic nerve and optic chiasm.

The capsule of the tumor was aspirated with a fine needle; no cystic fluid or blood was obtained. By means of a pointed knife blade the capsule of the tumor was incised for 1.25 cm., and a portion of the presumed tumor was scooped out with a pituitary spoon. This material was pale, grayish white and grumous. A report by Dr. A. C. Broders on a frozen section stated that the tissue resembled a

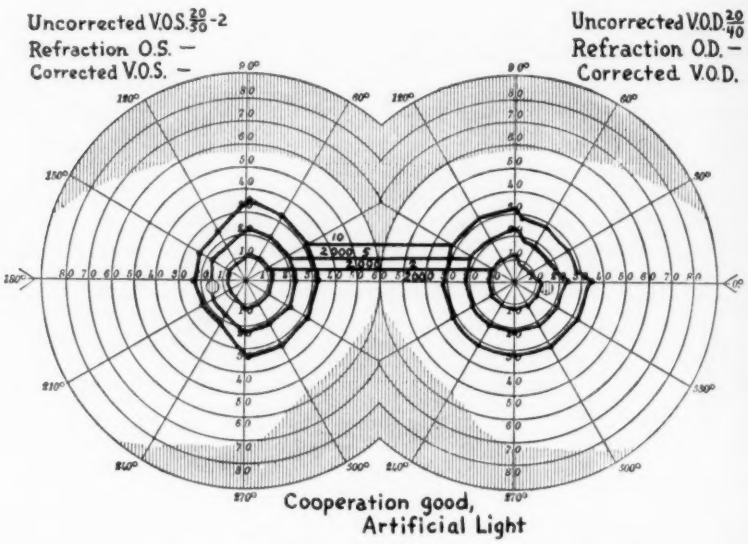

Fig. 2.—Early postoperative visual fields (June 25, fifteen days after operation). There has been satisfactory recovery from the bitemporal field defects, especially on the left side. Vision in the previously almost blind left eye has improved to 20/50—2 acuity.

tuberculoma, with epithelioid and giant cells. The intracapsular mass was then attacked with the glass suction apparatus, pituitary scoops and biting rongeurs until thorough removal had been carried out. By gentle traction on the collapsed walls of the capsule it was possible to free the left optic nerve completely and, to a certain extent, the right optic nerve.

The dura was completely resutured with fine interrupted silk sutures, and the bone flap was replaced. The scalp was likewise resutured with fine interrupted silk sutures in the galea and the skin. The patient was returned to her room in satisfactory condition.

Course.—The immediate period of convalescence was uneventful. The temperature (rectal) was elevated to 102.2 F. on the first postoperative day, but subsided rapidly thereafter to normal. Visual fields taken on the fifteenth post-

operative day (fig. 2) showed considerable widening of the fields bilaterally as compared with the preoperative appearance, together with great improvement in vision in the previously almost blind left eye.

The final[1] histologic diagnosis, after examination of the fixed sections by special stains (Dr. Broders), was "diffuse noncaseous tuberculosis of the pituitary gland" (fig. 3). The patient left the hospital for her home in excellent condition on June 26, 1936, the sixteenth postoperative day.

The patient was readmitted on Nov. 27, 1936 for a diagnostic lumbar puncture and was discharged on the following day. This procedure was carried out under considerable difficulty, and complete relaxation of the patient was questionable. The initial pressure was 275 mm. of water; the spinal fluid was clear and colorless; 8 cc. was removed for examination, after which the pressure was 210 mm.

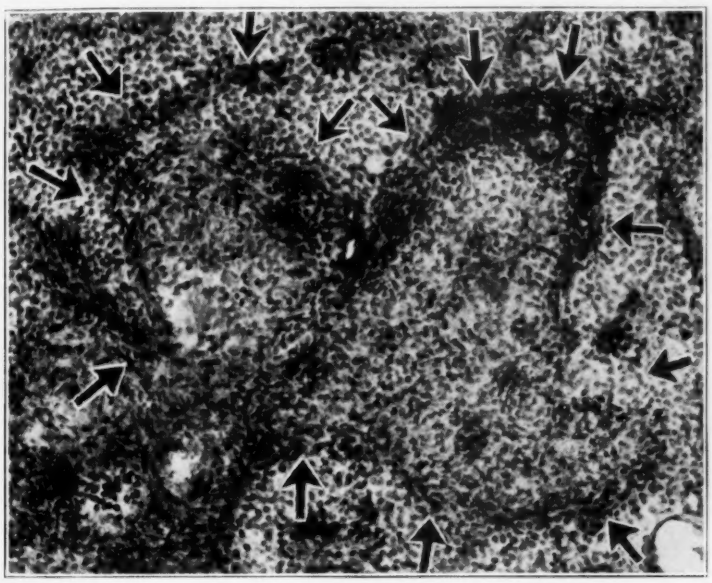

Fig. 3.—Photomicrograph (× 160) of the pituitary tissue removed at operation, demonstrating noncaseous tuberculosis of the pituitary gland. The large area in the center, shaped approximately like a cloverleaf (arrows), consists of a ring of lymphocytes (small dark cells constituting the border) inside which is a conglomerate mass of tubercles containing several giant cells. At the top center is seen a single giant cell surrounded by normal pituitary tissue.

of water. The spinal fluid gave a negative Wassermann reaction and contained 3 white cells per cubic millimeter (2 lymphocytes and 1 polymorphonuclear leukocyte), 88 mg. of dextrose and 692 mg. of chlorides per hundred cubic centimeters.

1. A later communication from Dr. Broders (Dec. 13, 1939) stated that he regarded the lesion as "noncaseous diffuse tuberculosis (not a tuberculoma) of the pituitary gland, of low virulence and comparable to the so-called sarcoid of Boeck," which, histologically, is a noncaseating, diffuse tuberculous-like lesion in which the tubercle bacilli cannot be demonstrated. The sarcoid of Boeck also is practically, if not entirely, unknown in the pituitary gland.

The patient has been examined several times by one of her referring physicians between operation and the time of writing (December 1939); he reports that her vision has steadily improved since operation. The visual fields and visual acuity (of each eye) are now within normal limits (fig. 4). Reports of the patient's postoperative condition follow:

On Oct. 8, 1936 (four months after operation) a letter from Dr. Cabaniss stated: "Vision was 20/20 in the right eye and 20/20—2 in the left eye. Both visual fields were practically normal for white and all colored test objects, except for a very slight left upper temporal defect. The fundal vessels were normal, and the optic disks showed no increase in pallor. The pupillary reflexes were normal, as were the responses of all the other cranial nerves. All tests for cerebellar function, including station and gait, were normal."

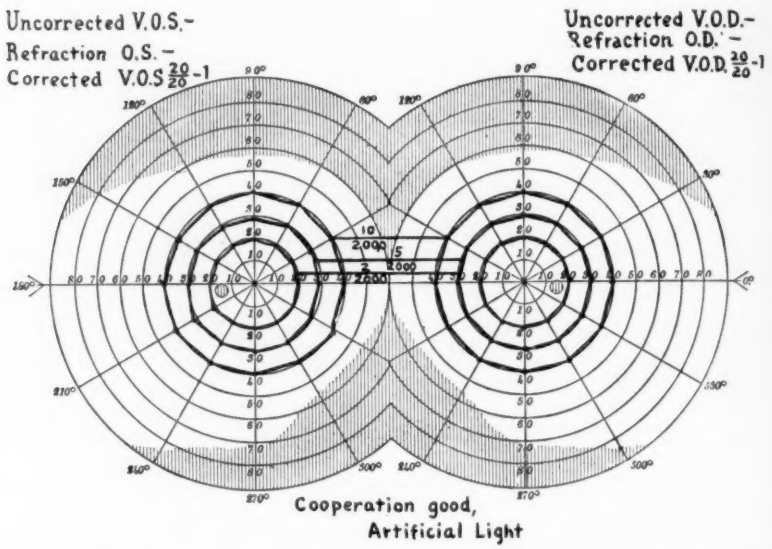

Fig. 4.—Later postoperative visual fields (May 3, 1939, almost three years after operation). Satisfactory visual acuity and full visual fields (bilaterally) have been maintained to date. (These visual fields were plotted from data furnished by Dr. J. Lawson Cabaniss.)

On June 19, 1937 Dr. Cabaniss wrote that he had examined the patient on April 14, 1937 (ten months after operation), at which time her vision was 20/20—1 in the right eye and 20/20—2 in the left. The visual fields were within normal limits, as were the results of examination of the fundi. The general health was good.

On June 16, 1937 (one year after operation) the patient wrote that she was in excellent health. She had no headache, and vision was reported to be 100 per cent in each eye. She had gained a great deal of strength during the two months prior to her report and engaged in her usual household duties.

On Aug. 27, 1937 (fourteen months after operation) the patient's son stated, during a visit to one of our clinics, that his mother was "doing very well." She

had no headache, vision was excellent and she had continued her usual work without interruption since her letter to us two months previously.

The last report from the patient (Nov. 15, 1939, forty-one months after operation), in response to a follow-up letter, stated: "Last spring, I went to see Dr. Cabaniss, and he said my vision was 100 per cent [approximately three years after operation]. I read a great deal, and my eyes seem strong now. I do my housework without difficulty, and I feel that the operation was a wonderful success."

Repeated requests during the last three years for the patient to visit one of our clinics in person for a complete neurologic examination have been unsuccessful, for the patient says that the distance is too great and that transportation is not available.

COMMENT

Rarity of the Lesion.—A careful review of the literature for the last thirty years has not disclosed a similar case on record; indeed, the lesion appears to be unique. In 1937 and subsequently, an inquiry was made by letter of practically all neurosurgical clinics in the United States and Canada, as well as of a number of excellent neuropathologists; no case at all similar to that just described has been reported. One neurosurgeon stated that he "had seen but 1 case of tubercle of the hypophysis, but the patient did not survive operation."

A few of those interrogated reported having observed a gumma of the pituitary gland at operation or at necropsy. The possibility that the lesion in our case was of this type appears unlikely in view of the histologic picture and the negative Wassermann reactions of the blood and spinal fluid. Dr. Bernard Alpers stated that he had never seen a report in the literature of diffuse tuberculosis or tuberculoma of the pituitary gland (confined to the hypophysis), and that he had not encountered it in a series of 200 tumors of the pituitary body, including those in the collection of the late Dr. C. H. Frazier, which he had examined personally. Tuberculosis of the pituitary gland, as part of tuberculous meningitis, was mentioned as having been seen by several who responded to our letter of inquiry, but our patient was and remains free of tuberculosis elsewhere than in the hypophysis, so far as we can determine.

Cushing,[2] in his two books devoted to disorders of the pituitary body and the hypothalamus, covering a period of over twenty years, made no mention of tuberculosis of any type involving these structures and, in a personal interview with one of us (J. M. M.) in 1938, stated that he did not recall ever having seen tuberculosis of the pituitary gland as an isolated surgical lesion.

Compaired,[3] in 1914, reported, apparently, the same case in a Spanish and in a French periodical. Study of the French article,[3b] however,

2. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912; Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

3. Compaired, C.: (*a*) Un caso de tuberculosis local de la pituitaria; curación, Siglo méd. **61**:82, 1914; (*b*) Un cas de tuberculose locale de la pituitaire, Rev. hebd. de laryng., 1914, pp. 487-491.

revealed that the case was not one of intracranial (pituitary) tuberculosis; the word "pituitaire," as used by Compaired, refers to the nasal fossa and not to the contents of the sella turcica at all. His case was really one of nasal tuberculosis; the lesion was in the right anterior nasal fossa, and only local treatment in this region was necessary. In French parlance, the term "pituitary membrane" is synonymous with the nasal (schneiderian) membrane. Roentgen examination of the sella turcica was not made on Compaired's patient, nor was a craniotomy performed. The patient, a 20 year old woman with headache, difficult breathing through the right nostril and epistaxis, was free from tuberculosis elsewhere in the body. Compaired removed the granulations from the right nasal fossa by curettement and galvanic cauterization; the lesion was apparently cured two years later. Photomicrographs of the tissue removed showed giant and epithelioid cells, regarded as "manifest proof of the tuberculous nature of the lesion" (Dr. R. Mata).

Letchworth [4] (1924) discussed a case of tuberculoma of the pituitary body in which the sella turcica appeared normal on roentgen examination. The patient had a sustained septic temperature (100 to 103 F.) for three weeks before death. At necropsy an isolated tuberculous mass was observed surrounding the pituitary body (not recorded as involving the gland itself), the optic chiasm and the adjacent portions of both optic nerves and tracts; the mass extended into the left orbit through the optic foramen.

The rarity of the single tuberculous lesion in the intracranial cavity is demonstrated by the statistics of Cushing,[5] who in a series of 2,023 cases of verified intracranial tumor (1932) had only 24 cases of such a lesion (11 cerebellar, 5 pontile and 8 cerebral), none of which was in the pituitary body. He stated that tuberculomas of the brain are more apt to be single than multiple.

Bailey [6] emphasized that tuberculosis causes two types of involvement of the central nervous system: (*a*) isolated tubercle of the brain and (*b*) tuberculous meningitis. One of his patients (fig. 148 and reference 6 of his book) had a single tuberculoma of the left cerebral peduncle.

Simmonds [7] reported 4 cases of tuberculosis of the pituitary gland, in all of which tubercle bacilli were observed in the pituitary gland and demonstrated post mortem in patients with tuberculosis elsewhere, as in the lungs or bones. He stressed that tuberculosis is apt to lodge in the posterior lobe when it occurs hematogenously (this is also true of all metastatic lesions in the pituitary gland). Simmonds made no mention of enlargement of the sella in his cases or, indeed, of gross enlargement of the pituitary gland.

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4. Letchworth, T. W.: Tuberculoma of the Pituitary Body, Brit. M. J. **1**:1127, 1924.

5. Cushing, H.: Intracranial Tumours, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 116.

6. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 403-406.

7. Simmonds, M.: Ueber Tuberculose der Hypophysis, Centralbl. f. allg. Path. u. path. Anat. **25**:194-197, 1914.

Kraus,[8] although reporting no case of isolated tuberculosis of the pituitary gland, stated that most instances of hypophysial tuberculosis are due to blood-borne metastases. In a few cases the disease progresses from neighboring areas of tuberculosis in the midbrain and the meninges or from tuberculous caries of the base of the skull.

Finally, Simmonds,[9] in discussing the occurrence of nonspecific giant cells in the hypophysis, said he had observed histologic changes in the anterior lobe of the pituitary body resembling tuberculosis but not due, apparently, to tuberculous infection. He reported 5 cases; all of his patients were women, varying in age from 49 to 73, whose pituitary glands were examined post mortem. In no instance, however, was the pituitary body enlarged. A number of lesions illustrated in his article greatly resembled tuberculosis histologically, but Simmonds refused to consider them as such, as he was unable to demonstrate tubercle bacilli in any of them.

Thus it is seen that in none of the cases cited was any lesion demonstrated that was at all similar to that in our case.

Rarity of Recovery.—A number of the neurosurgeons and neuropathologists answering our inquiry expressed surprise that in our case tuberculous meningitis did not develop; this fear was uppermost in our minds also, in view of Cushing's statement [10] that tuberculous meningitis is almost certain to follow within three months after the removal of a tuberculoma (from the cerebellum [11]).

Cushing [12] stated the belief that the cerebral tuberculous lesions have a better prognosis than the cerebellar; he reported a case in which a tuberculoma was excised from the left temporal lobe of a woman stenographer aged 29, under the assumption that it was a firm (astrocytomatous) glioma. It was found, when sectioned and studied, to be a fairly well organized tuberculoma. Five years later the patient was in perfect health. The primary source of the tuberculoma could not be found, nor was any mention made in the case report that tubercle bacilli were demonstrated.

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8. Kraus, E. J.: Die Hypophyse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, pp. 859-861.

9. Simmonds, M.: Ueber das Vorkommen von Riesenzellen in der Hypophyse, Virchows Arch. f. path. Anat. **223**:281-290, 1917.

10. Cushing,[5] p. 114.

11. One of us (C. C. C.) removed, on Dec. 15, 1933, a tuberculoma from the right cerebellar hemisphere of a physician aged 27, who had at the time a high degree of increased intracranial pressure. The patient also had pulmonary tuberculosis, which is still minimally active. At present (December 1939), six years after operation, he is otherwise well. The optic disks are normal, and there is no nystagmus. He has no headache, and the area of suboccipital decompression is collapsed and flat. All tests for cerebellar function give normal results. He continues on active duty as a staff physician in a tuberculosis sanatorium. Evidently the intracranial lesion was a single one, as occasionally occurs.

12. Cushing,[5] pp. 116-117.

Before Cushing's final report on his series of tumors of the brain, Van Wagenen [13] (1927) reported 17 cases of intracranial tuberculomas observed at the Peter Bent Brigham Hospital, in 6 of which the lesion was exposed and extirpation accomplished or attempted. All the 6 patients died within fifteen months of operation of intracranial or some other form of tuberculosis, although they all made satisfactory primary recovery from the operation itself. Another patient (case 16) was still doing well six years after suboccipital exploration, in which a supposed tuberculoma, not histologically verified, was demonstrated; decompression alone was done. All the lesions reported by Van Wagenen were in the cerebrum, cerebellum or brain stem; no instance of tuberculosis of the pituitary gland was recorded.

Cushing, in commenting on Van Wagenen's paper,[13] stated:

> The recoverability of these lesions depends a great deal on whether they are bovine or not. Doubtless the bovine cases are much more favorable than others; but pathologists do not really attempt to distinguish between human and bovine tuberculosis under the microscope. It is a difficult matter even by culture. Should one be fortunate enough to encounter a bovine tuberculoma . . . from which the organisms have died out, the conditions would be most favorable for surgical removal should pressure symptoms exist.

Vincent,[14] under a somewhat misleading title, related his experiences with 34 instances of tuberculoma of the brain, which occurred in a total of 1,348 cases of histologically verified tumors (2.5 per cent). The tuberculomas, listed according to location, were as follows: single cerebellar (18 cases), multiple cerebellar (3 cases), cerebral (10 cases) and lesions of the brain stem (3 cases). In 28 of the 34 cases operation was done. In 6 of the 9 cases of cerebral tuberculoma in which operation was performed there was immediate cure, which followed complete removal of the growth in 4 and decompression alone in 2 instances. Three of the patients with tuberculoma of the cerebellum who were operated on were cured, although it was not stated whether the lesion was removed or whether decompression alone was performed. Of the other patients, some died at the time of operation, others of tuberculous meningitis following operation and the remainder of extracranial systemic tuberculosis. Vincent did not state whether tubercle bacilli were found in the tuberculomas which he removed, but stressed the fact that macroscopically and microscopically the structure of the lesions was identical with that of tuberculomas elsewhere in the body. He recorded no instance of tuberculosis of the hypophysis in his series of cases.

Bailey [6] also stated that any attempt at removal of an intracranial tuberculoma is almost always followed by tuberculous meningitis; decompression alone should be done, followed by sanatorium care. All authorities are in general agreement with this statement.

We fully expected, after the histologic identification of tuberculosis of the hypophysis (in the supposed pituitary tumor), that our patient would probably die of tuberculous meningitis, especially as the lesion was basilar and undoubtedly communicated widely with the basilar cisterns.

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13. Van Wagenen, W. P.: Tuberculoma of the Brain, Arch. Neurol. & Psychiat. **17**:57-92 (Jan.) 1927.

14. Vincent, C.: Sur les tubercules cérébraux, Ann. méd.-chir. **3**:151-156, 1938.

In all of the cases of tuberculosis of the pituitary gland that we have encountered in the literature or in answer to our letter of inquiry the condition has been varified at postmortem examination as an isolated lesion, as part of tuberculosis elsewhere, or as incident to tuberculous meningitis, with one exception, a case reported by one of the neurosurgeons interrogated by letter, whose patient did not survive operation.

SUMMARY

A case of diffuse noncaseous tuberculosis of the pituitary gland, associated with enlargement of the sella turcica, primary optic atrophy and bitemporal hemianopia, in which the growth simulated tumor of the pituitary body and in which the postoperative survival period has been three and one-half years, is reported. The disease occurred apparently as an isolated lesion in the hypophysis. At the time of writing, the patient remains in excellent health, and the severe bitemporal headache and serious visual impairment, which existed before operation, have entirely disappeared.

A thorough review of the literature of the last thirty years, together with an inquiry of a large number of neurosurgeons and certain neuropathologists, has revealed no similar case on record.

NOTE.—The one objection to designating as tuberculosis the lesion discussed in this presentation is that the tubercle bacilli have never been demonstrated in the tissue removed at the time of operation, either by examination of stained sections or by guinea pig inoculation. This point will be raised, of course, by all pathologists. However, the legend for figure 3, describing the histologic picture, expresses the opinion of Dr. A. C. Broders, of the Mayo Clinic, who examined the original tissue and supplied the photomicrograph, and of Dr. James Cash, professor of pathology, and Dr. C. R. Tuthill, neuropathologist, at the University of Virginia School of Medicine, who also examined the photomicrograph and stated that the picture is consistent with a histologic diagnosis of diffuse tuberculosis of the pituitary gland. Furthermore, Cushing,[12] Vincent,[14] Van Wagenen [13] and others have described tuberculous lesions of the brain diagnosed on a histologic basis only, without demonstration of the tubercle bacilli. Hypophysial gumma, the only other condition with which this lesion might be confused histologically, has been rather adequately excluded by negative Wassermann reactions of the blood and spinal fluid, together with the absence of clinical signs suggesting syphilis.

The German papers of Kraus [8] and of Simmonds [9] relate entirely to nonsurgcial cases studied post mortem, in none of which was the sella enlarged, the histologic findings being demonstrated in the routine examination of necropsy material.

CYST OF THE PULVINAR OF THE THALAMUS

Report of a Case with Obstructive Internal Hydrocephalus and Diabetes Mellitus of Intermittent Severity

W. T. Niemer, M.Sc., and A. R. Vonderahe, M.D., Cincinnati

The following case is reported because of a particularly puzzling clinical course in which the glycosuria and hyperglycemia varied in intensity with the intensity of clinical manifestations of episodes of internal hydrocephalus. At autopsy, a fluctuant cyst of the pulvinar of the thalamus obstructing the aqueduct of Sylvius was found. In addition, there appeared other symptoms and signs, some of which are explained on the basis of a detailed anatomic analysis of the central nervous system.

REPORT OF CASE

L. M., a white woman aged 63, was admitted to the Hamilton County Home and Chronic Disease Hospital on June 27, 1936 and died on August 25, 1936. There was mental confusion, making it difficult to obtain a satisfactory history from the patient. The husband stated that up to ten years prior to admission to the hospital the patient had been normal, with normal speech, emotions and mentality. Approximately ten years prior to her admission slight weakness developed in the legs and gradually became worse. Her husband also recalled that some time later weakness developed in her right arm, which after moderate use became numb until it was rested again. She did not otherwise complain of numbness or tingling. About a year prior to admission it became necessary for her to seek assistance in walking by using chairs or other objects for support. Ten months prior to admission to the hospital she also began to complain of a bearing-down feeling associated with urgency in urination. She underwent an operation at the Good Samaritan Hospital in June 1935 for repair of a cystocele. After this operation weakness in the legs steadily increased; she began to complain of occasional pains in the arms and of numbness in the legs. The husband noticed that she became depressed.

A diagnosis of diabetes was made for the first time in April 1936, two months prior to admission. On June 25 a note from Dr. C. Striker called attention to mild diabetes, arteriosclerosis and cystocele. There were no symptoms referable to the cardiorespiratory system. No gastrointestinal difficulty was noted aside from a tendency to constipation.

Physical Examination.—At the time of entrance to the Hamilton County Home and Chronic Disease Hospital the lungs were clear on percussion and auscultation. The heart was of normal size; its rhythm was regular, and there were no murmurs. The pulse rate was 126; the blood pressure was 135 systolic and 85 diastolic. Numerous nevi were present on the abdominal wall. The patient was obese. The liver and spleen were not felt. No areas of tenderness or muscle spasm were noted. On vaginal examination a slight cystocele was found. There were numerous lacerations of the cervix. The uterus was normal.

From the Department of Anatomy (Neurology), University of Cincinnati College of Medicine and the Medical Service of the Hamilton County Home and Chronic Disease Hospital.

Neurologic examination revealed pupils of equal size, which reacted to light and distance. There was no disturbance of ocular movements. Ophthalmoscopic examination revealed normal disks and early arteriovenous compression. A doubtfully positive Babinski sign was noted on the right. Urinalysis gave a 4 plus reaction for sugar. The fasting blood sugar value was 240 mg. per hundred cubic centimeters. The spinal fluid was clear, colorless and under normal pressure and presented 3 cells per cubic millimeter and a negative reaction for globulin (Pandy). The Wassermann reaction of the blood and of the spinal fluid was negative. The differential blood count revealed 52.3 per cent neutrophils, 2.3 per cent stab cells, 0.7 per cent eosinophils, 0.7 per cent basophils, 35 per cent lymphocytes and 9 per cent mononuclear cells.

Course.—The patient received insulin from June 29 to July 31. The dose was 15 international units a day until July 21 and 12 units a day from then to July 31. On July 31 an additional 10 units was given. A blood sugar determination made on June 30 showed 242 mg. per hundred cubic centimeters; with the administration of insulin this was reduced to 130 mg. per hundred cubic centimeters by July 6. On July 31, however, in spite of the regular doses of insulin, a blood sugar determination revealed 250 mg. per hundred cubic centimeters. Ten additional units of insulin was therefore ordered, but this not only failed to bring about a reduction of the blood sugar but actually was associated with a rise to 496 mg. per hundred cubic centimeters on the following day, August 1. At this time there were mental confusion, lethargy, a temperature of 100.5 F., nausea, vomiting and marked difficulty in expression of language. In retrospect, this alteration of the clinical picture appears to have been associated with an acute exacerbation of internal hydrocephalus.

On August 1 the administration of insulin was discontinued altogether, and a low caloric diet (1,190 calories) was prescribed. There was remission of the signs of internal hydrocephalus, with absence of nausea and vomiting and return of some mental clarity. This period of comfort continued to August 24, when the following signs and symptoms developed. There was increasing drowsiness, followed by stupor and coma, without, however, evidence of acetone on the breath. The pupils were pinpoint and no longer reacted to light or distance. There were loss of the use of the right arm and incomplete paralysis of the face. The deep reflexes were present in the arms, with questionable increase on the left. The abdominal and patellar reflexes were absent. The Babinski sign and other pathologic reflexes were not elicited. There was an excessive amount of sugar in the urine, and the blood sugar reading was 296 mg. per hundred cubic centimeters. The temperature increased at hourly intervals to 108 F. There was a gradual increase in the pulse and respiratory rates. Although 30 units of insulin was given on August 24, the blood sugar reading was 325 mg. per hundred cubic centimeters on the following day, when the patient died.

It can be noted from this record that there appeared two episodes in which the clinical picture was indicative of internal hydrocephalus and that during these episodes the administration of insulin not only was not effective in altering the level of the blood sugar but, on the contrary, was associated with an elevation of the amount. It may also be noted that remission of the clinical signs of internal hydrocephalus on the first occasion was associated with a pronounced diminution of the signs of diabetes.

Postmortem Observations.—Autopsy was performed by Dr. D. A. Nathan three and one-half hours after death. The anatomic diagnosis was: cyst of the left thalamus, with obstructive internal hydrocephalus; cerebral edema and con-

gestion; acute cystitis; ureteritis and pyelonephritis; renal calculi; aortic and coronary atherosclerosis; early chronic emphysema; fibrosis of the ovaries; myocardial fibrosis; chronic endometritis and endocervicitis; fatty infiltration of the liver, and toxic changes in the viscera. The fresh brain weighed 1,100 Gm.

Gross examination of the brain after fixation in a solution of formaldehyde revealed moderate atheromatous changes in the vessels at the base of the brain. The pia-arachnoid membrane was slightly clouded. The veins draining into the superior sagittal sinus were tortuous and congested. The convolutions were flattened. The fissures were narrowed to the point of obliteration. Horizontal section through the brain revealed dilatation of the lateral ventricles. A cyst

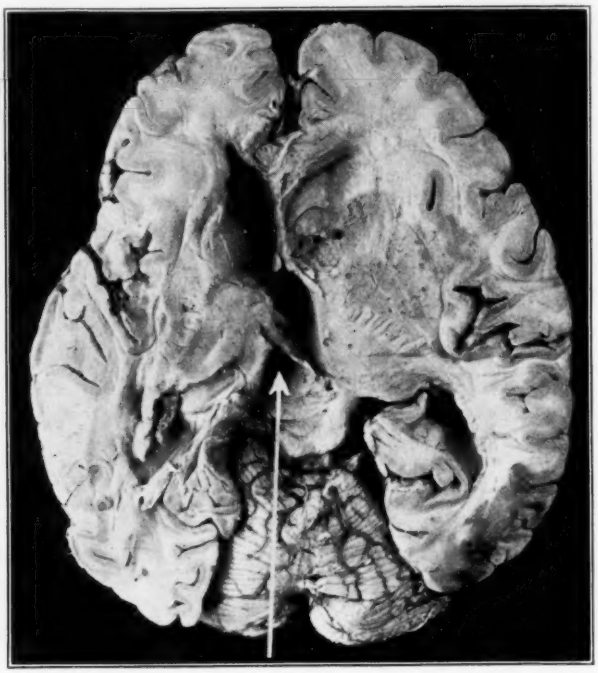

Fig. 1.—Horizontal section through the brain after fixation in a solution of formaldehyde, showing the posterior extent of the cyst (indicated by arrow), with pressure effects on the quadrigeminal plate and aqueduct of Sylvius, and the dilated third and lateral ventricles.

(fig. 1) with a smooth wall was observed extending anteriorly to implicate the posterior and medial portions of the left thalamus and posteriorly to overlap the quadrigeminal plate and the aqueduct of Sylvius. There was obliteration of the normal markings of the anterior and posterior quadrigeminal bodies. The third ventricle was greatly dilated and pushed to the right.

Serial sections were made through the diencephalon, the entire brain stem and the cerebellum and through several cortical areas. The sections were stained with cresyl violet and with Morgan's method.[1]

1. Morgan, L. O.: Iron Hematoxylin as a Myelin Sheath Stain and Neutral Red Ripened by Colon Bacillus as a Nerve-Cell Stain, Anat. Rec. **32**:283, 1926.

The cyst observed at autopsy began anteriorly in the midportion of the medial nucleus of the thalamus on the left side and extended posteriorly to the posterior border of the left superior colliculus (fig. 2). It extended laterally to the internal medullary lamina and medially to the wall of the third ventricle, without, however, rupturing into this cavity. In general, therefore, the immediate structural involvement included the quadrigeminal plate, the superior part of the tegmentum of the midbrain, a part of the medial nucleus of the thalamus and a large part of the medial and posterior portions of the pulvinar.

The pressure within the cyst was apparently intense enough to cause intermittent and finally permanent internal hydrocephalus of the third and lateral ventricles by obstruction of the aqueduct of Sylvius. At the time of death there was fusion of the ependymal cells of the aqueduct (fig. 2).

Examination of serial sections revealed destruction and compression of various structures. Beginning anteriorly and proceeding posteriorly, the following structural

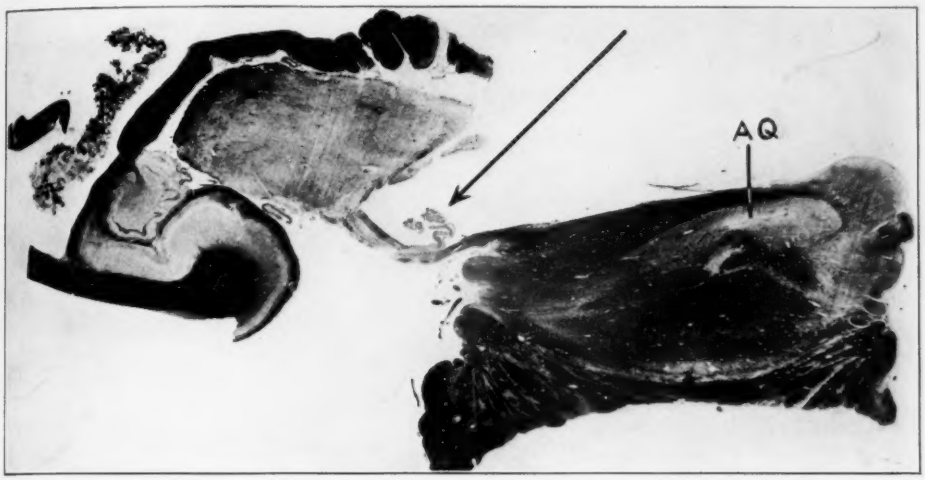

Fig. 2.—Frontal section through the brain stem at the level of the superior colliculus, showing the cyst (indicated by arrow), blocking of the aqueduct of Sylvius (*AQ*) by fusion of the ependymal lining, destruction of the medial two thirds of the pulvinar, absence of the left superior colliculus and compression of the right superior colliculus, demyelination of the deep fiber stratum of the left superior colliculus and distortion and malalinement of tegmental structures. Morgan's stain; × 2.4.

implications were noted: The floor of the third ventricle was markedly attenuated. The mamillary bodies were pulled away from the midline, and the supramamillary commissure appeared considerably stretched. The lateral nucleus of the thalamus was compressed and presented degeneration of its medial part in its whole anteroposterior extent (fig. 3). Symmetric discrete areas of demyelination were noted in the midportion of the ventral part of the basis pedunculi on both sides (pressure effects from the tentorium cerebelli); in addition, there was some diffuse demyelination of the left basis pedunculi. The red nucleus and corpus subthalamicum were definitely flattened (fig. 3). The centrum medianum was almost entirely destroyed on the left. The medial two thirds of the left pulvinar thalami was

replaced by the cyst, and degeneration was noted in the lateral outflow of fibers from the pulvinar (figs. 2 and 3). Both habenular areas were destroyed (fig. 3). The superior and inferior colliculi were absent on the left and intensely compressed on the right. The deep fiber stratum of the left superior colliculus was demyelinated. The periaqueductal gray matter was distorted, and tegmental structures, such as the medial longitudinal fasciculus, the trochlear nucleus and the dorsal tegmental nucleus, had lost their normal symmetric relations. The lateral part of the basis pontis presented an extremely irregular contour (fig. 2).

By a system of cell counting devised by Morgan,[2] the status of various vegetative nuclei of the anterior portion of the hypothalamus was determined. The table gives the results of this determination.

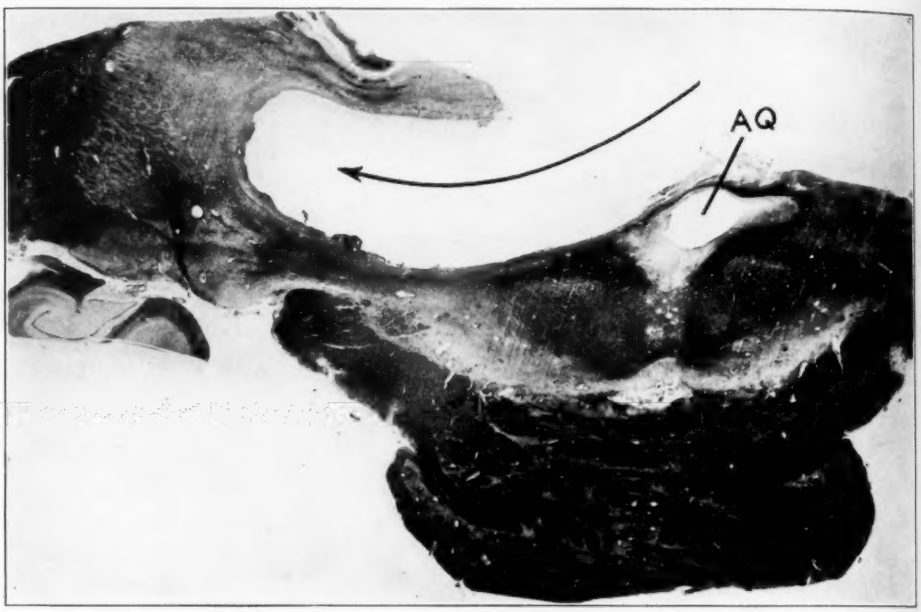

Fig. 3.—Frontal section through the brain stem at the level of the aqueduct of Sylvius and the red nucleus, showing the cyst (indicated by arrow), the distorted aqueduct of Sylvius (*AQ*), the effects of pressure on the lateral nucleus of the thalamus, the symmetric areas of degeneration in the basis pedunculi on both sides, flattening of the red nuclei and destruction of the habenular region. Morgan's stain; × 2.5.

Cell Counts of Nuclei of the Hypothalamus

	Cell Loss, per Cent	Normal Cells Remaining, per Cent
Nucleus paraventricularis	30	33
Nucleus supraopticus	0	35
Substantia grisea	50	33
Nucleus tuberis lateralis	49	55
Nucleus tuberomamillaris	Slight	38

2. Morgan, L. O.: Personal communication to the authors.

Serial sections through the angular gyrus revealed a consistent streak of degeneration of the white matter at the base of the gyrus running at right angles to the two lips of the gyrus. These degenerative fibers were regarded as representing the pathway from the pulvinar to the angular gyrus.

A microscopic area of softening was noted in the cortex of the left cerebellar hemisphere.

The pancreas appeared normal both grossly and microscopically.

COMMENT

Signs of aphasia and mental confusion made their appearance early, apparently as a result of the primary involvement of the pulvinar, while diabetes and hyperthermia occurred rather late. It is also to be noted that glycosuria, hyperglycemia and hyperthermia were closely associated, especially on two occasions when the patient suffered acute exacerbations of symptoms indicative of internal hydrocephalus. The hyperglycemia and glycosuria showed a pronounced increase in severity with the onset of the clinical signs of internal hydrocephalus and a decrease in intensity with the lessening of these signs. It cannot be stated what the cause of the diabetes may have been. Cell counts of hypothalamic nuclei, however, gave a characteristic picture of cell loss, as previously noted by Morgan, Malone and Vonderahe [3] in other cases of diabetes. Assuming that the cause of diabetes is not known, it can be stated that the intensity of diabetes appeared to vary with the intensity of the hydrocephalic pressure on diencephalic structures.

A case of atypical diabetes mellitus in which the patient, though in coma, did not present the usual dehydration commonly found in diabetic acidosis was reported by Byrom and Russell.[4] In this case the condition was associated with a colloid cyst of the roof of the third ventricle which obstructed the foramen of Monro and caused internal hydrocephalus. As in the case under discussion, large doses of insulin failed to reduce the high sugar content of the blood.

The bilateral destruction of the habenular nuclei may, according to Papez,[5] be sufficient to produce hyperthermia, since evidence exists that these nuclei are concerned with the elimination of heat. It is to be noted also that pathologic changes and cell loss occurred in various hypothalamic nuclei (see table) and that pathologic alterations in the hypothalamic area may also have played a role in the disturbances of temperature control.

Weakness of the extremities, particularly of the right arm, can be traced to pressure on the left lateral nucleus of the thalamus, the tegmentum of the midbrain and the left basis pedunculi.

3. Morgan, L. O.; Malone, E. F., and Vonderahe, A. R.: Pathologic Changes in the Hypothalamus in Diabetes Mellitus, J. Nerv. & Ment. Dis. **85:125, 1937.**

4. Byrom, F. B., and Russell, D. S.: Ependymal Cyst of the Third Ventricle Associated with Diabetes Mellitus, Lancet **2:278, 1932.**

5. Papez, J. W.: Personal communication to the authors.

According to Ariëns Kappers, Huber and Crosby;[6] Minkowski;[7] Clark and Boggon,[8] and Foix and Nicolesco,[9] the pulvinar is not a reception nucleus for visual impulses. In the opinion of these authors, it has a new portion connected with the association areas of the occipital and parietal cortex (angular gyrus) and an older portion related anatomically to the superior colliculus and the gray matter around the posterior commissure. Rundles and Papez[10] described cases in which the pulvinar was entirely absent, secondary to destruction of the temporal lobe. Speech difficulty and amentia characterized these cases clinically. The patient in the present case likewise presented inability to remember and think in a consecutive manner.

The peculiar language difficulty observed in this case apparently resulted from a number of factors. It will be noted that, in addition to incoherency of thought, there was also a motor difficulty in speech. The lack of fluency of perception and of thought may be ascribed to the lesion encountered in the pulvinar. The difficulty of movement of the mouth and pharynx in the acts of speaking and swallowing may be traceable to the lesion in the centrum medianum. According to Papez and Rundles,[11] this nucleus is a way station for oropharyngeal impulses to the corpus striatum, which, in turn, receives cortical impulses for the control of chewing, swallowing and articulate speech.

SUMMARY

A case is reported of a cyst of the left pulvinar thalami which obstructed the anterior orifice of the aqueduct of Sylvius. The affected portions of the angular gyrus, hypothalamus, subthalamus, thalamus and midbrain are described and correlated with the clinical symptoms. The clinical signs and symptoms included atypical diabetes mellitus, which varied in intensity, apparently with the degree of internal hydrocephalus; ataxic speech; amnesia; dementia; various motor and sensory difficulties, and terminal hyperthermia.

6. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, vol. 2, p. 1152.

7. Minkowski, M.: Étude sur les connexions anatomiques des circonvolutions rolandiques, pariétales et frontales, Schweiz. Arch. f. Neurol. u. Psychiat. **12**:277, 1923; **14**:255, 1924; **15**:97, 1924.

8. Clark, W. E. L., and Boggon, R. H.: The Thalamic Connections of the Parietal and Frontal Lobes of the Brain in the Monkey, Phil Tr. Roy. Soc., London, s.B **224**:313, 1935.

9. Foix, C., and Nicolesco, J.: Les noyaux gris centraux et la région mésencéphalo-sous-optique, Paris, Masson & Cie, 1925.

10. Rundles, R. W., and Papez, J. W.: Fiber and Cellular Degeneration Following Temporal Lobectomy in the Monkey, J. Comp. Neurol. **68**:267, 1938.

11. Papez, J. W., and Rundles, R. W.: Dorsal Trigeminal Tract and the Centre Median Nucleus of Luys, J. Nerv. & Ment. Dis. **85**:505, 1937.

PNEUMOCEPHALUS

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Fractures involving the frontal sinus and the ethmoid cells occasionally allow the escape of air into the cranial cavity. According to Rawling,[1] a few cases have been discovered by roentgen examination in which a pocket of air has become locked intracranially, usually between the dura and the frontal lobe. In the case now reported, however, there was sufficient air to fill the lateral ventricles and the traumatic porencephalic cysts in both frontal lobes.

REPORT OF A CASE

History.—P. H. G., a man aged 47, incurred a fracture of the skull on July 30, 1939, when the truck in which he was riding collided with another vehicle. Before the accident, he had been employed at clerical work; he was apparently in good health, including freedom from any visual difficulties. He was unconscious after the injury, but recovered consciousness during the night. On the following morning Dr. Paul Gallagher performed right subtemporal decompression.

On August 3 the patient's general condition was very poor; he had severe chills and high temperature. By August 7 his condition had greatly improved, owing to the use of sulfanilamide.

A roentgenogram of the skull on August 22 disclosed a linear fracture of the left frontal bone, extending into the frontal sinus, with probable damage to the cribriform plate. There was no evidence of air within the skull.

On September 2 the patient blew his nose and "felt as if he had blown out a clot." After this incident clear liquid began to drain from his nose; he is said to have remarked that he felt as if there were air in his head. Soon afterward there developed chills and a temperature of 105 F. Sulfanilamide was again administered. The patient's general condition improved, and in about a week the discharge of fluid from the nose ceased. On October 4 he walked out of the hospital and went to his home; he seemed cheerful and rational, although he was unable to see well.

About October 9 he became restless and mentally dull. He was unable to bend his knees when he attempted to assume a sitting posture; arm movements were unimpaired, but his legs were weak and spastic, and there was incontinence of urine. Lumbar punctures on October 11 and 13 were reported to show clear fluid

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From the Neuropsychiatric Section, William Beaumont General Hospital, El Paso, Texas. The patient was referred by Dr. Paul Gallagher, of El Paso.

1. Rawling, L. B.: Head Injuries, London, Oxford University Press, 1934, p. 23.

without any gross evidence of increased pressure. However, a manometric reading was not made.

Examination.—The patient was admitted to the William Beaumont General Hospital on Oct. 14, 1939. He was then bedridden, had incontinence of urine and was unable to talk except for an occasional word. The heart and lungs were normal; the blood pressure was 132 systolic and 82 diastolic.

Neurologic examination disclosed mental impairment, dulness, mild intellectual and emotional deficit and motor aphasia. There was marked disturbance of verbal formulation, manifested by inability to name common objects in the standard tests for aphasia described by Head.[2] Auditory word recognition was well preserved. The patient presented complete loss of sense of smell bilaterally; complete blindness of the left eye, with limitation of vision to a small nasal field of the right eye; bilateral primary optic atrophy; unequality and fixation of the pupils, the left being slightly larger than the right; paralysis of the right sixth cranial nerve, and weakness of involuntary movements of the muscles of the right side of

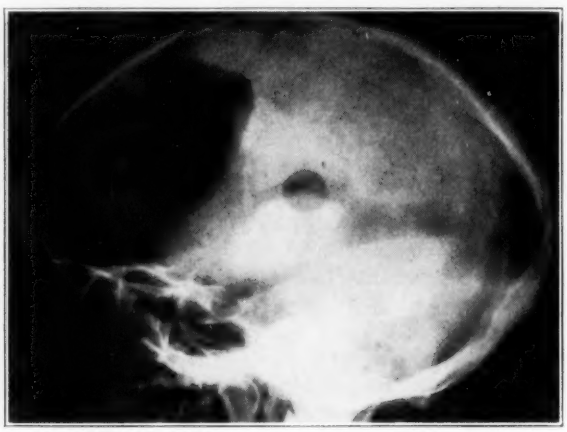

Fig. 1.—Lateral roentgenogram of the skull.

the face. There was lack of spontaneous movements of the extremities, without paralysis. The patient was unable to relax the muscles controlling the fingers after grasping objects. The tendon reflexes of the lower extremities were practically absent. There was incontinence of urine and occasionally of feces.

Routine laboratory tests gave negative results except for plus-minus Wassermann and Kahn reactions of the blood on three occasions. (Twenty years before the patient had been treated for a syphilitic infection.)

On October 18, roentgen examination revealed a linear fracture emerging from the left base of the anterior cranial fossa and extending upward and backward through the left frontal bone to the coronal suture. This was clearly shown in the anteroposterior view. Both anteroposterior and lateral roentgenograms of the skull showed a remarkable amount of air in the ventricular system. The anterior horns of both ventricles were dilated and appeared to communicate with large porencephalic cysts of the frontal lobes (fig. 1).

2. Head, H.: Aphasia and Kindred Disorders of Speech, New York, The Macmillan Company, 1926, vol. 1, p. 150.

On October 23 roentgen examination disclosed no change in the amount of air in the ventricles or in the porencephalic cysts, but on November 1 there appeared to be increased cavitation of the frontal lobes, especially the right. The clinical symptoms and signs persisted; the patient's general mental impairment increased, and he became incontinent of both urine and feces.

At Dr. Gallagher's request, Dr. Samuel Ingham presented the case at a special clinic at the annual meeting of the Southwestern Medical Association on Novem-

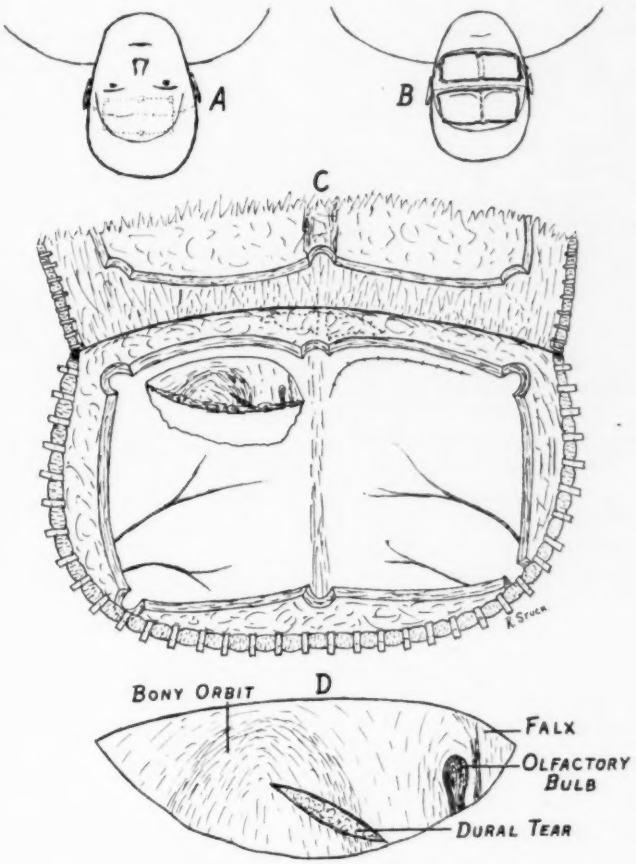

Fig. 2.—Diagrams illustrating stages in the operation.

ber 11. It was his opinion and our own that the case was one of fracture of the skull, with a persistent sinus tract extending from the cerebral ventricular system into the nose, the evidence being that air, fluid and a fluid level could be seen in the roentgenograms of the skull and that definite cerebrospinal rhinorrhea had been reported.

It was concluded that the sinus tract should be obliterated by a craniotomy and a fascial transplant over the dural defect.

Operation.—On November 12 a bilateral frontal osteoplastic craniotomy was performed (fig. 2 *A* and *B*), with the patient under anesthesia induced by avertin with amylene hydrate (R. S.). The dura in the frontal region appeared normal. On the right a horizontal incision was made in the dura just over the orbit (fig. 2 *C*). The frontal pole was tense against the dura. A brain needle was passed into the frontal lobe. At a depth of about 1 cm. air came from the needle and the brain fell away. Exploration of the under surface of the right frontal lobe revealed no dural rent in the anterior cranial fossa.

A similar incision and dissection were made on the left side. On the anteromedial surface of the bony orbit the brain was observed to be adherent. After dissection with cotton pledgets, a dural rent was discovered, 3/16 inch (4.5 mm.) wide and 5/8 inch (15.8 mm.) long (fig. 2 *D*).

Capt. C. W. Hardy removed a piece of fascia lata, about 3/4 inch (1.9 cm.) wide and 1 inch (2.54 cm.) long, from the left thigh. This was laid over the dural defect in the subdural space, and the brain was allowed to expand against it and hold it in place. The bone flap was wired in place, and the wound was closed in layers with interrupted black silk sutures without drainage.

Outcome.—Convalescence was uneventful, without elevation of temperature. A roentgenogram of the skull made on Nov. 20, 1939 no longer showed air. Incontinence of urine gradually lessened and disappeared in about ten days. Examination three weeks after operation disclosed no evidence of aphasia. The patient walked about and engaged in all ordinary physical activities without difficulty. Several weeks after operation confusion as to time relations, memory for recent events and the amount of a sum of money was observed, but the patient readily accepted the corrections made by his relatives.

Residual symptoms and signs include total blindness of the left eye and marked restriction of the visual field in the right eye which is limited to the nasal side and pushed farther to the left by the internal strabismus of the right eye, due to persistent paralysis of the right sixth cranial nerve. The pupils continue to be inactive to light and in accommodation; the knee jerks and ankle jerks are still unobtainable. The sense of smell is still absent bilaterally.

COMMENT

Pneumocephalus is an uncommon sequel of skull fracture.[3] It has, however, been reported occasionally, with varying amounts of air within the skull. The air usually reaches the cranial cavity by extension through a fracture into an air sinus. It may also enter directly through a compound fracture of the skull.

In this case, an enormous amount of air reached the cranial cavity from the nose, long after the time of the original injury. Sulfanilamide probably prevented the patient from dying of meningitis that developed after the initial trauma, as well as subsequently.

Blindness, in the absence of roentgenographic evidence of damage to the occipital lobes, is probably based on direct damage—either traumatic or vascular—to the optic tract.

It is believed that trauma may be established in this case as a cause of porencephaly of the frontal lobes. The patient was performing highly

3. Dandy, W. E.: Pneumocephalus (Intracranial Pneumatocele or Aerocele), Arch. Surg. **12**:949-982 (May) 1926. Lewis, A. J.: Traumatic Pneumocephalus, Brain **51**:221-243, 1928.

technical clerical work prior to his injury, and it seems improbable that the cavitation of both frontal lobes of the brain could have existed before the accident.

The operative repair of dural rents with pneumocephalus has undergone several developments. Formerly,[3] attempts were made to obliterate the sinus tract from outside the dura by means of tissue transplants and sclerosing procedures. The persistent pressure from within the cranial cavity, however, caused leaks, and the repairs were occasionally unsuccessful. Recently, Naffziger [4] has shown the necessity of repair from within the cranial cavity, the transplant being placed in the subdural space over the dural rent.

SUMMARY AND CONCLUSIONS

A case is reported of unusually extensive pneumocephalus with traumatic porencephalic cysts in both frontal lobes, occurring more than one month after fracture of the skull, as a result of which the air reached the cranial cavity from the nose.

The dural defect was repaired by a transplant of fascia lata in the subdural space immediately over the defect.

Motor aphasia and incontinence of urine were abolished and general mental impairment was greatly relieved by surgical intervention, after an illness of more than two months.

4. Naffziger, H. C.: Personal communication to the authors.

PROLONGED COMA AND CEREBRAL METABOLISM

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The vulnerability of the brain to lack of either dextrose or oxygen is one of its outstanding characteristics. It has been previously demonstrated that the chief foodstuff of the brain is carbohydrate.[1] During insulin hypoglycemia, when the brain is deprived of its substrate, cerebral metabolism is necessarily depressed, with resulting changes in function.[2] The effects of a short period of hypoglycemia are readily reversible by the administration of carbohydrate. After prolonged hypoglycemia, however, permanent cerebral damage may occur, with irreversible functional changes, such as pareses of various types.[3] When oxygen is not available for the utilization of dextrose the metabolism of the brain cannot proceed, and the symptoms of anoxia in many respects resemble those of hypoglycemia. When anoxia is of short duration the symptoms are entirely reversible;[4] when it is more prolonged permanent damage may result.[5] Different parts of the brain vary in susceptibility to injury when metabolism is depressed by hypoglycemia and anoxia. As a rule, parts which are phylogenetically newer are the first to suffer changes.[2]

Irreversible changes resulting from hypoglycemia [6] and anoxia occur not infrequently, but as yet no studies have been made of the cerebral metabolism of patients under these conditions. The present report is

This study was aided by a grant from the Child Neurology Research (Friedsam Foundation).

From the Department of Physiology and Pharmacology, Albany Medical College, Union University, Albany, N. Y., and the Psychiatric Division, Bellevue Hospital, New York.

1. Himwich, H. E., and Nahum, L. H.: Am. J. Physiol. **101**:446, 1932. Lennox, W. G.: Cerebral Circulation: Respiratory Quotient of Brain and of Extremities in Man, Arch. Neurol. & Psychiat. **26**:719 (Oct.) 1931.

2. Himwich, H. E.; Frostig, J. P.; Fazekas, J. F., and Hadidian, Z.: Am. J. Psychiat. **96**:371, 1939.

3. Himwich, H. E.; Fazekas, J. F.; Bernstein, A. O.; Campbell, E. H., and Martin, S. J.: Proc. Soc. Exper. Biol. & Med. **39**:244, 1938.

4. Himwich, H. E.; Alexander, F. A. D., and Lipetz, B.: Proc. Soc. Exper. Biol. & Med. **39**:367, 1938.

5. Gildea, E. F., and Cobb, S.: Effects of Anemia on Cerebral Cortex of Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930. Andreev, L. A.: Functional Changes in Brain of Dog After Reduction of Cerebral Blood Supply: Disturbance of Conditioned Reflexes After Ligation of Arteries, ibid. **34**:699 (Oct.) 1935. Yant, W. P.; Chornyak, J.; Schrenk, H. H.; Patty, F. A., and Sayers, R. R.: Studies in Asphyxia, Public Health Bulletin 211, United States Treasury Department, Public Health Service, 1934.

6. Tannenberg, J.: Am. J. Path. **15**:25, 1939.

concerned with results obtained in a study of 4 patients who died: 1 of hypoglycemia, 2 of carbon monoxide poisoning and 1 of uremic coma.

METHOD

Samples of blood from the internal jugular vein and the femoral artery were collected and analyzed for oxygen.[7] Measurements of blood pressure were made in all cases. The sugar content of the blood was determined for the patient in case 1, who was suffering from posthypoglycemic coma, and the nonprotein nitrogen of the blood and the circulation time for the patient in case 4, who had mercury bichloride poisoning. The results are presented in the accompanying table.

Hematologic Data on Four Patients Who Died in Coma

			Oxygen Content, Volume per Cent						
Patient	Diagnosis	Date	Arterial	Venous	Difference	Average Difference	Blood Pressure, Mm. of Mercury	Comment	
1	Posthypoglycemic coma	2/15/39	.....	.....	....	....	122/90	On admission	
		3/20/39	14.28	11.18	3.10	....	130/90	Blood sugar 250 mg. per 100 cc. (after intravenous administration of dextrose)	
		3/20/39	13.60	11.18	2.42	2.76	.....		
2	Carbon monoxide	1/15/39	.....	.....	....	....	120/60	On admission	
		1/20/39	16.68	13.60	3.08	....	168/68		
		1/21/39	15.52	13.12	2.40	3.05	158/40		
		1/22/39	14.70	11.02	3.68	....	178/78		
3	Carbon monoxide	7/28/39	.....	.....	....	....	112/70	On admission	
		7/29/39	18.41	16.62	1.79	1.79	110/74		
								Circulation Time, Sec.	Nonprotein Nitrogen, Mg. per 100 Cc.
4	Mercury bichloride poisoning	8/ 5/39	.....	.....	....	....	90/60	On admission	27
		8/ 9/39	12.64	7.32	5.32	....	120/76	10.2	72
		8/11/39	12.56	11.56	1.00	....	176/64	10.0	75
		8/12/39	12.06	10.16	1.90	1.64	122/80	10.0	130
		8/12/39	12.17	10.35	1.82	....	.....	12.8	96

REPORT OF CASES

CASE 1.—The patient was diabetic and had a localized infection. Coma was precipitated when the dose of protamine zinc insulin was not reduced after infection was eliminated by surgical intervention. When first observed by us, the patient was experiencing a series of recurrent convulsions. Despite intravenous injection of dextrose, which raised the level of blood sugar to above normal, the convulsions continued until the patient died. Two sets of blood samples taken between convulsive episodes revealed an average arteriovenous difference in the oxygen content of cerebral blood of 2.76 volumes per cent, a value much reduced as compared with the average normal value of 7.43 volumes per cent.

This low arteriovenous difference in the oxygen content of cerebral blood was probably secondary to irreversible cerebral changes produced by the prolonged deprivation of dextrose previous to intravenous medication.

7. Van Slyke, D. D., and Neill, J. M.: J. Biol. Chem. **61**:523, 1924.

CASES 2 and 3.—Two patients who had been exposed to carbon monoxide fumes were admitted to the hospital in deep coma. The first patient was flaccid, with depressed reflexes. She was examined on three successive days before her death, and an average arteriovenous difference in oxygen contents of 3.05 volumes per cent was observed. The second patient was spastic, presenting a picture resembling decerebrate rigidity. His oxygen utilization was 1.79 volumes per cent.

The brains of these 2 patients had been subjected to a prolonged period of anoxia, but at the time of the biochemical observations both patients were practically free of carbon monoxide. Thus, in contradistinction to the small arteriovenous difference, the oxygen content of the arterial blood of the second patient (case 3) was within normal limits, indicating a plentiful supply of oxygen to the brain. The low arteriovenous difference in the oxygen content of the cerebral blood must therefore be attributed to damage previously inflicted by the inhalation of carbon monoxide. The relatively lower arterial oxygen content of the first of these patients (case 2) was, nevertheless, adequate to furnish the normal quota of oxygen if the brain had been capable of utilizing it.

CASE 4.—The patient had ingested mercury bichloride with suicidal intent and died in uremia. An observation, made four days after admission but while the patient was still in contact with his environment, revealed that the nonprotein nitrogen value of the blood had risen from 27 to 72 mg. per hundred cubic centimeters and that the arteriovenous difference in the oxygen content of cerebral blood was 5.32 volumes per cent. Three observations made after contact was lost showed an average oxygen utilization of 1.64 volumes per cent.

COMMENT

The small arteriovenous differences in the oxygen content of cerebral blood observed in these 4 patients may be explained equally well by increased cerebral blood flow and by diminished cerebral metabolism. The observations permit no decision as to which of the two alternatives is correct. However, a review of the literature makes it unlikely that the small arteriovenous differences can be explained by more rapid flow of blood through the brain. It would require the improbable rise in blood flow of from two and a half to four and a half times the normal rate to cause such an increase, and the brain is an organ which has a relatively constant blood flow.[8] Forbes and Cobb[9] emphasized the importance of blood pressure in determining cerebral blood flow; the changes in blood pressure in these patients cannot explain such an increase in blood flow. Certainly, in case 4 there was not a marked change in the systemic blood flow as indicated by the circulation time. It is therefore possible that the low arteriovenous differences in the oxygen supply of cerebral blood for these 4 patients may be attributed to changes in the brain, changes secondary to lack of energy required for maintenance.

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8. Lennox, W. G.: Constancy of Cerebral Blood Flow, Arch. Neurol. & Psychiat. **36**:375 (Aug.) 1936.

9. Forbes, H. S., and Cobb, S.: Brain **61**:221, 1938.

SUMMARY

A study was made of the cerebral metabolism of 4 patients who died in coma of three types. In 1 coma was secondary to hypoglycemia, in 2 others it was the result of the inhalation of carbon monoxide and in the fourth uremia was produced by the ingestion of mercury bichloride. In each of these 4 patients the arteriovenous difference in the oxygen content of the cerebral blood was diminished. The significance of this diminution is discussed.

DECEREBRATE TONIC EXTENSOR CONVULSIONS AS A SIGN OF OCCLUSION OF THE BASILAR ARTERY

Report of a Case with Autopsy

MICHAEL SCOTT, M.D., AND H. C. LENNON, M.D., PHILADELPHIA

The following case is reported because it suggests that an obstruction of the blood flow in the basilar artery must be considered as a cause of decerebrate tonic extensor convulsions (or so-called cerebellar fits) in man.

Pollock and Davis (1923 and 1924) [1] were able to produce decerebrate attacks in cats by ligation by the basilar and carotid arteries but not by ligation of either alone. White [2] repeated their experiments on dogs and found that the method did not produce decerebration in the dogs and that it was necessary in addition to ligate all branches of the carotid bulb in the neck on both sides, as well as the common carotid arteries and the basilar artery.

We have been unable to find any reports on the production of decerebrate attacks by ligation or interruption of the blood flow in the basilar artery alone.

Pines and Gilinsky [3] reviewed 17 cases of thrombosis of the basilar artery reported up to 1932. Hyland [4] and Hofer [5] also reported their cases. None of these authors mentioned decerebrate or tonic convulsions as a symptom of thrombosis of the basilar artery. However, Környey [6] Gintrac, Nothnagel, Luce and others [7] have reported tonic and clonic convulsions associated with pontile hemorrhage in human beings. We were unable to find a report in the literature of a case similar to ours.

Presented before the Philadelphia Neurological Society, Oct. 27, 1939.

From the Department of Neurology and Neurosurgery, headed by Dr. Temple Fay, and the Department of Pathology, headed by Dr. L. W. Smith, Temple University School of Medicine.

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2. White, R. R.: Experimental Methods of Production of Decerebrate Rigidity in Dogs by Vascular Occlusion of Basilar Artery, J. Nerv. & Ment. Dis. **85**:663-667 (June) 1937.

3. Pines, L., and Gilinsky, E.: Thrombosis of the Basilar Artery and Vascularization of Pons, Arch. f. Psychiat. **97**:380-387, 1932.

4. Hyland, H. H.: Thrombosis of Basilar Artery, Arch. Neurol. & Psychiat. **30**:342-356 (Aug.) 1933.

5. Hofer, I.: Ménière's Syndrome Due to Thrombosis of Basilar Artery of Cerebrum, Monatschr. f. Ohrenh. **68**:533-538 (May) 1934.

6. Környey, S.: Rapidly Fatal Pontile Hemorrhage, Arch. Neurol. & Psychiat. **41**:793-799 (April) 1939.

7. Gintrac, Nothnagel, Luce and others, cited by Környey.[6]

REPORT OF CASE

History.—A woman aged 35 was admitted to Dr. Fay's service at the Temple University Hospital in status epilepticus. Eleven days previously, eight teeth had been extracted because of apical infection. Two days after the extraction the oral temperature was 101 F., and the patient complained of vomiting, anorexia and weakness. A physician prescribed strychnine sulfate, 1/60 grain (1 mg.), three times a day for two days, but this gave no relief. She continued to vomit and remained bedridden for nine days. On the tenth day of her illness her temperature rose to 104 F. by mouth; she became stuporous, and convulsions began in which both upper and lower extremities became markedly rigid in the extensor position. She was then admitted to the hospital for study.

Examination.—The temperature was 101.4 F. by rectum, the pulse rate 120, the respiratory rate 30 and the blood pressure 134 systolic and 100 diastolic. The patient appeared to be unconscious but blinked spontaneously, and the eyes and mouth were held partly open. The swallowing reflex was present, and there was skew deviation of the eyes. The pupils were equal in size and were slightly constricted. There was indrawing of the supraclavicular space on inspiration. The head was retracted, and the upper extremities were in rigid extension, with internal rotation and flexion at the wrists. This rigidity could be broken only with difficulty. The lower extremities were also in extensor rigidity, with the feet in extreme plantar flexion. At times the rigidity relaxed, and the deep tendon reflexes were found bilaterally hyperactive and equal on the two sides. There were active Babinski and Chaddock signs bilaterally. The eyegrounds, examined after a mydriatic was used, showed no choking of the disks or definite vascular pathologic change. The patient at times would open her eyes, look at the examiner, attempt to speak and then lapse into unconsciousness.

Lumbar puncture showed clear fluid, which was under a pressure of 8 mm. of mercury. Repeated blood counts during three days showed a normal red cell count and normal concentration of hemoglobin, but the white cell count was between 18,000 and 20,000 per cubic millimeter, with from 90 to 93 per cent polymorphonuclear cells. The sugar, calcium and phosphorus contents of the blood and the carbon dioxide–combining power were normal. The chloride and urea nitrogen levels of the blood were slightly elevated. Roentgenograms of the skull and chest were normal. Electrocardiographic studies showed anoxemia of the cardiac muscle and tachycardia. Cultures of material from the gums and tooth sockets revealed many viridans and hemolytic streptococci. Blood cultures taken during the patient's fifth day in the hospital, when the temperature reached 104 F. by rectum, showed Streptococcus viridans. Previous to this, blood cultures taken on two consecutive days had been sterile. The Wassermann reaction of the blood was strongly positive (4 plus). The spinal fluid on admission showed 4 lymphocytes per cubic millimeter and 67 mg. of protein, 50 mg. of sugar and 795 mg. of chlorides per hundred cubic centimeters, and the Wassermann reaction was strongly positive (4 plus). The colloidal gold curve was 5544431000. Examination of the spinal fluid repeated on the fifth day revealed a cell count of 60 cells per cubic millimeter, all of which were lymphocytes, and the Wassermann reaction was again strongly positive (4 plus).

Course.—The patient's temperature gradually increased to 106 F.; she became progressively more stuporous and died on the fifth day after admission.

Autopsy (H. C. L.).—The external structures were normal. The heart weighed 270 Gm. and was slightly dilated. The myocardium was moderately softened.

There were no mural thrombi. The valves appeared normal except for dilatation of their orifices. The abdominal aorta contained a few atheromatous plaques. Microscopic sections showed chronic myocardosis and early coronary sclerosis.

Gross microscopic sections of the lungs revealed small areas of pulmonary hemorrhage, with diffuse bronchopneumonia.

The kidneys were normal grossly, but microscopic sections revealed mild congestion, with some tubular degeneration.

The spleen was slightly enlarged. Microscopic sections showed marked fibrosis of the stroma, similar to that seen in congenital syphilis.

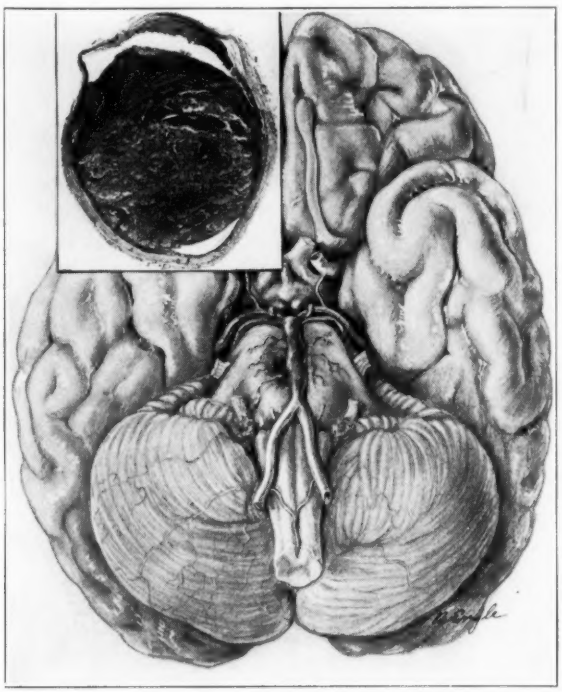

Fig. 1.—Sketch of the brain showing the thrombosed basilar artery. Insert, cross section of the thrombosed basilar artery.

The liver was grossly normal. Microscopic sections showed slight congestion and early fatty infiltration.

When the dura of the brain was opened a large amount of clear cerebrospinal fluid escaped. The vessels over the superior surface of the brain showed marked engorgement. There was thickening of the pia-arachnoid about the base of the brain. There were softening and hemorrhagic discoloration of the under surface of the pons. The basilar artery was thrombosed throughout its entire length (fig. 1). The vertebral arteries, branches of the basilar artery, internal carotid arteries and vessels making up the circle of Willis were all free from thrombosis. Gross and microscopic sections of the pons revealed diffuse hemorrhagic areas throughout, with softening and beginning necrosis (fig. 2).

Microscopic sections from the base of the brain showed moderate small round cell infiltration into the subarachnoid spaces (fig. 3 *A*). The cerebrum showed no gross or microscopic lesions, except for moderate perivascular cuffing about the blood vessels (fig. 3 *B*).

Stains for bacteria revealed no organisms in the basilar artery.

COMMENT

This case offered a problem in differential diagnosis. The decerebrate tonic attacks suggested the possibility of (1) tumor of the cerebellum or

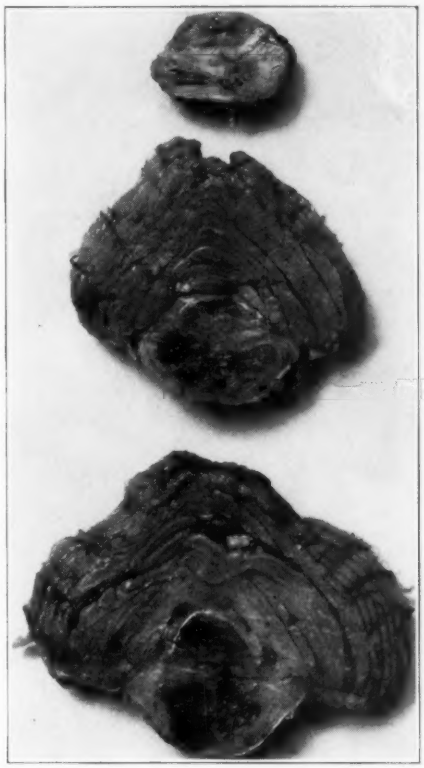

Fig. 2.—Cross sections of the pons, medulla and cerebellum, showing hemorrhagic infarction.

posterior fossa, (2) tetanus, (3) strychnine poisoning (especially since the patient had been taking the drug, $\frac{1}{60}$ grain [1 mg.] by mouth three times a day, for two days during the early part of her illness), (4) hypoglycemia (since she had eaten little) and (5) tetany and alkalosis (because of the prolonged vomiting).

Cerebellar tumor was ruled out by the rapid onset, the absence of choked disks, the high temperature and the high white cell count of the blood; tetanus, by the absence of an infected wound, the absence of constant trismus and the presence of stupor; strychnine poisoning, by

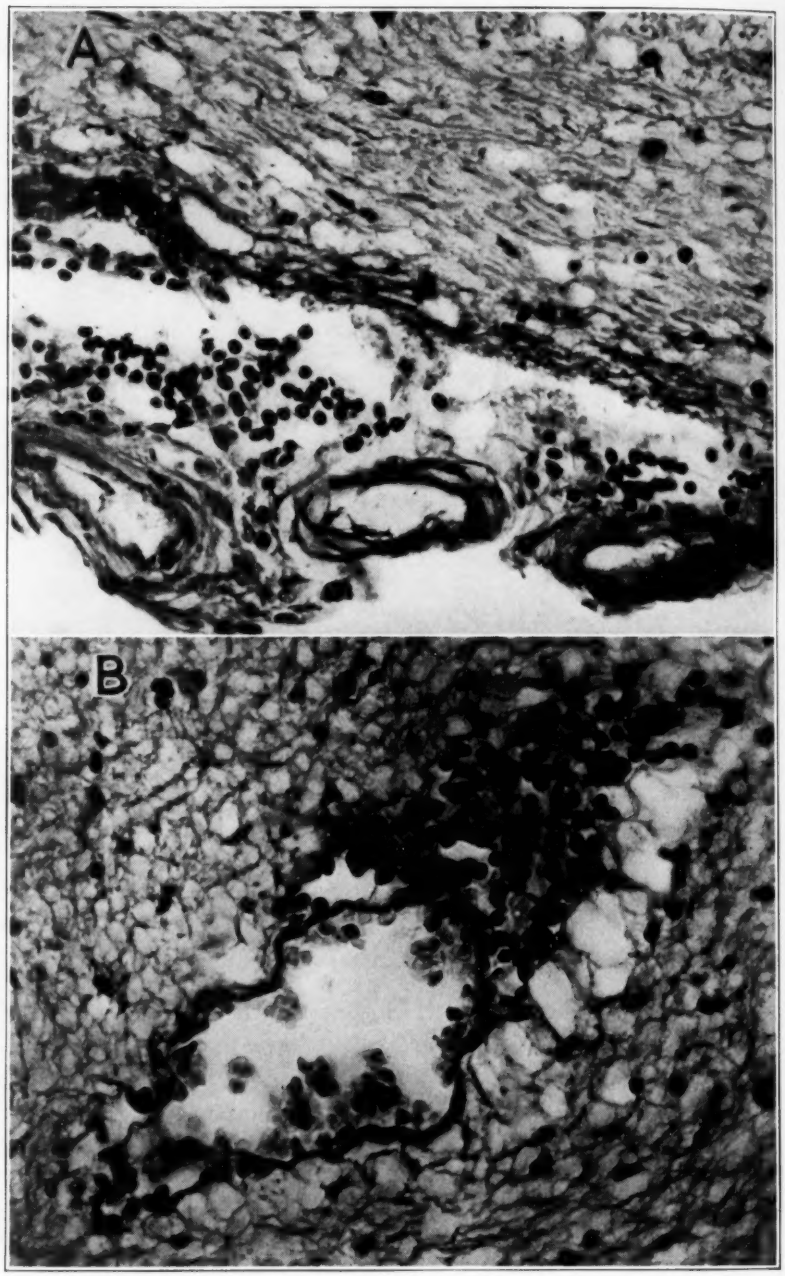

Fig. 3.—*A*, cellular infiltration of the meninges; *B*, perivascular infiltration of the cerebral vessels.

the small dose taken, the stupor, the high temperature and the high white cell count; hypoglycemia, by the normal blood sugar content, and tetany and alkalosis, by the absence of the Chvostek sign and the normal calcium and phosphorus content and the normal carbon dioxide-combining power of the blood.

The positive Wassermann reaction of the blood and of the spinal fluid and the first zone type of the colloidal gold curve finally gave a clue to the etiologic factor; syphilis probably was responsible for the thrombosis of the basilar artery. However, microscopic studies of this artery did not show any of the characteristic signs of syphilitic invasion. Since Str. viridans was found in the tooth sockets and recovered from the blood while the patient was alive, it is possible that this organism may have played a part in producing the vascular lesion.

CONCLUSION

We believe that this case proves that tonic decerebrate extensor attacks in man may be produced by complete interruption of the blood flow through the basilar artery. Although in our case the cause of the obstruction was thrombosis of the artery, it is conceivable that a protracted spasm of the artery causing obstruction of the lumen or selective failure of blood to reach the basilar artery might also produce tonic decerebrate attacks. Perhaps one of these mechanisms causes the tonic phase of the classic grand mal convulsion.

DISCUSSION

DR. L. M. WEINBERGER, Philadelphia: This is an extremely provocative case—provocative in the sense that it raises the question of decerebrative rigidity in man. The term "decerebration" is a misnomer, in that merely because the contraction of the extremities and retraction of the neck mimic the state observed in animals with a severed brain stem it does not necessarily mean that same condition exists in man. As a fact, it has been pointed out by several authorities that there is in the literature no report of an authenticated case of actual decerebration in man. The nearest approach to actual decerebration has been seen in cases of pineal tumor.

The term "decerebrate rigidity" in relation to human beings originated, I think, in the papers by Wilson, published in the 1920's, in which he described the condition in man and the underlying pathogenesis.

One obtains the picture of so-called extension rigidity, but actually it is not decerebrate rigidity. If it were, it would be found in a number of instances of lesions of the brain stem, in which there is the closest approach to anatomic discontinuity. In the cases of tumors of the midbrain reported by Dr. Alpers and Dr. Watts several years ago one would have expected so-called decerebrate attacks and rigidity to appear, but they did not.

I am interested in knowing what studies have been made on the cortex, because in a few cases of streptococcic infection, such as that described, or in syphilis, it would be possible to have widespread cortical damage which might explain the extensor rigidity.

DR. MICHAEL SCOTT, Philadelphia: Dr. Lennon could not see any microscopic evidence of syphilis in the thrombosed artery. Bacterial stains of the artery did not show any organisms. In the study of the cortex Dr. Lennon observed perivascular cuffing with lymphocytes in some areas. The changes that one might expect in advanced neurosyphilis were not present.

With regard to the proper use of the terms decorticate and decerebrate: It is my impression that the patient showed signs of decerebration, as evidenced by the tonic extensor type of convulsions. I do not know of any other way clinically to classify the attacks. Perhaps physiologists can help to differentiate decerebrate and decorticate convulsions.

Dr. Weinberger does not believe that the decerebrate attacks can occur in the case of a lesion involving the pons. Magnus, Bazett and Penfield (in Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, page 153) "found that decerebrate rigidity persisted as one proceeded caudally with coronal sections until a point just rostral to the vestibular nuclei. A section several centimeters caudal to this abolishes decerebrate rigidity."

Technical and Occasional Notes

CEREBRAL DYSRHYTHMIAS IN RELATIVES OF EPILEPTIC PERSONS

LEON J. ROBINSON, M.D., PALMER, MASS.

The problem of hereditary factors in epilepsy has long been an important one. Lennox, Gibbs and Gibbs [1] pointed out that "only one epileptic person in five is able to name any relative who has been similarly affected." Yet these observers found abnormal electroencephalograms in 54 per cent of 138 relatives of patients with epilepsy. The relatives comprised parents, children and siblings.

Löwenbach [2] obtained abnormal electroencephalograms for 17 of 37 nonepileptic relatives of 2 epileptic patients. Strauss, Rahm and Barrera [3] found abnormal electroencephalograms in 26.9 per cent of 93 relatives of 31 epileptic persons.

PRESENT STUDY

Electroencephalograms were obtained from 15 known epileptic patients and 36 of their nonepileptic relatives, consisting of 20 parents, 15 siblings and 1 maternal aunt. In all cases tracings were recorded during a period of quiet rest and during a six minute period of hyperventilation. None of the patients or relatives had a seizure during the recording.

Tracings were interpreted as abnormal if they contained any waves of 5 per second frequency or less, frequent 6 per second waves, wave and spike formation or groups of fast waves consistent with grand mal activity. Tracings were classified as doubtful if they contained rare 6 per second waves. Some observers [1] have also included as abnormal waves of a frequency below 9 or above 12 per second. In the present study the electroencephalograms have been interpreted in the light of broad criteria for normality, so that the incidence of abnormality may be estimated conservatively.

Of the 15 epileptic patients, 12 had idiopathic and 3 symptomatic epilepsy (due to birth injury in 2 cases and head trauma in 1). Twelve patients (11 with idiopathic epilepsy and 1 with symptomatic epilepsy due to birth injury) had abnormal electroencephalograms (waves of 5 per second or less), and 2 of these had wave and spike forms in addition. The electroencephalogram was doubtful in 1 case (of epilepsy following trauma to the head) and normal in 2 cases (1 of idiopathic epilepsy and 1 of symptomatic epilepsy due to birth injury). Prior to

From the Monson State Hospital.

1. Lennox, W. G.; Gibbs, E. L., and Gibbs, F. A.: The Inheritance of Epilepsy as Revealed by the Electroencephalograph, J. A. M. A. **113**:1002-1003 (Sept. 9) 1939.

2. Löwenbach, H.: Electroencephalogram in Healthy Relatives of Epileptics: Constitutional Elements in "Idiopathic Epilepsy," Bull. Johns Hopkins Hosp. **65**: 125-138 (July) 1939.

3. Strauss, H.; Rahm, W. E., Jr., and Barrera, S. E.: Electroencephalographic Studies in Relatives of Epileptics, Proc. Soc. Exper. Biol. & Med. **42**:207-212 (Oct.) 1939.

hyperventilation only 8 patients had an abnormal record; on hyperventilation an additional 4 patients showed abnormalities (waves of 5 per second or less).

Of the 20 parents tested, 10 included both the mother and the father of the patient. Both parents in 1 family and 1 parent in another had abnormal records (frequent 6 per second waves). Doubtful tracings (rare 6 per second waves) were obtained from both parents of 1 family group, and from 1 parent of each of 2 families, the other having a normal record.

Of the 10 unpaired parents (only 1 parent of the family group was tested), 3 had doubtful electroencephalograms (rare 6 per second waves), whereas the rest had normal records.

Of 15 siblings of the 15 epileptic patients, 9 had abnormal electroencephalograms, with waves of 5 per second or less, and 3 had doubtful records, with rare 6 per second waves.

One maternal aunt had an abnormal record (waves of 5 per second or less), while the patient and the patient's mother (sister of the aunt) had normal records.

The findings can be briefly summarized as follows: Of 15 epileptic patients, the electroencephalograms of 12 (80 per cent) were abnormal and that of 1 was doubtful. Of 36 relatives of the 15 epileptic patients, the electroencephalograms of 13 (36 per cent) were abnormal and those of 10 (27 per cent) were questionable. Thus, judged by broad criteria for normality, an appreciable number of this small group of relatives showed aberrant electroencephalograms.

COMMENT

Lennox, Gibbs and Gibbs [1] concluded that the cerebral dysrhythmia associated with epilepsy is inheritable; because it may be a dominant trait in the transmission of epilepsy they expressed the belief that if an epileptic person marries he should choose a person with normal brain waves.

Löwenbach [2] stated that the dysrhythmias in the relatives of epileptic persons are the expression of an inherited nonspecific functional instability of the nervous system, and that additional unknown factors must be present to make up clinical epilepsy. Osgood and I,[4] in a study of 38 institutionalized epileptic persons who, even in the absence of anticonvulsant medication, had been free of seizures for from five to thirty years, found that 65 per cent of them had grossly abnormal electroencephalograms. In these patients with persistent cerebral dysrhythmia we were unable to discover whether any factors, lost or acquired, had abolished seizures. It is known that cerebral dysrhythmia may and does occur in the absence of epileptic seizures. Thus, it may occur in some persons with schizophrenia or with severe behavior disorders, in relatives of epileptic patients, in some normal persons and possibly in association with other conditions still to be investigated. Nevertheless, it has been established that a significantly larger proportion of the relatives of epileptic persons have abnormal electroencephalograms than the very small number found in a sample of the general population.

4. Osgood, R., and Robinson, L. J.: Cessation of Epileptic Seizures and the Electroencephalogram, Arch. Neurol. & Psychiat. **43**:1007-1008 (May) 1940.

SUMMARY

Electroencephalograms were obtained from 15 epileptic patients and 36 nonepileptic relatives.

The relatives comprised 20 parents, 15 siblings and a maternal aunt. Of 15 epileptic patients, 12 (80 per cent) had abnormal electroencephalograms and 1 a doubtful tracing.

Of the 36 relatives, 13 (36 per cent) had abnormal electroencephalograms and 10 (27 per cent) questionable.

Judged by broad criteria for normality, cerebral dysrhythmia occurred in from one third to one half of this small group of nonepileptic relatives of epileptic persons.

News and Comment

SIGMUND FREUD MEMORIAL FELLOWSHIPS FOR PSYCHOANALYTIC TRAINING

The Boston Psychoanalytic Institute announces three additional Sigmund Freud Memorial Fellowships for Psychoanalytic Training, to begin September 1941. These fellowships are open to graduates of a recognized medical school who have had at least one year of general hospital training and two years' work in psychiatry, and cover tuition fees only.

One additional fellowship for training in applied nontherapeutic psychoanalysis will be open to those who have a Ph.D. degree or an equivalent degree in the field of anthropology, sociology, pedagogy or allied sciences.

For further information, please write immediately to Dr. M. Ralph Kaufman, chairman of the Educational Committee, Boston Psychoanalytic Institute, 82 Marlborough Street, Boston. Applications must be submitted before Feb. 1, 1941.

CORRECTION

In the article by Drs. Charles Davison and S. Philip Goodhart entitled "Monochorea and Somatotopic Localization," in the April issue (ARCH. NEUROL. & PSYCHIAT. **43**:792, 1940), the word "right" in the first line under "Conclusion," on page 802, should read "left," and in the next line the word "right" should be inserted preceding "caudate nucleus."

Abstracts from Current Literature

Anatomy and Embryology

ORIGIN AND SIGNIFICANCE OF BINUCLEATE PURKINJE CELLS IN MAN. WARREN ANDREW, Arch. Path. **28**:821 (Dec.) 1939.

Binucleate cells constituted from 3 to 4 per cent of the total number of cells in the cerebellum of a Negress, aged 22, who died of cerebrospinal syphilis. This is the only one of 40 specimens of human autopsy material examined by the author which showed such cells. The binucleate condition is the result of amitotic division of the nucleus into two equal, or almost equal, parts. Division of the nucleus is preceded by that of the nucleolus. In some instances there appears to be an abortive attempt at cytoplasmic division of the Purkinje cell, as evidenced by the separation of the dendrite trunks at their origin from the cell body. The binucleate condition of the Purkinje cell and the mode of division by which it is brought about seem to be essentially similar in man, rats and mice. The factors responsible for the division may, however, differ in degree or kind, since until the present time binucleate cells have been observed in man only in pathologic states, while in rodents they occur as a feature of normal senility. WINKELMAN, Philadelphia.

A STUDY OF THE FUNCTIONAL INNERVATION OF THE HYPOPHYSIS. G. W. HAIR and J. F. MEZEN, Endocrinology **25**:965 (Dec.) 1939.

Hair and Mezen investigated the functional relation between the parasympathetic component of the facial nerve and the hypophysis in adult rabbits by (*a*) electrical stimulation of the nerve at the geniculate ganglion and (*b*) bilateral destruction of the facial nerve. Stimulation of the facial nerve at the geniculate ganglion did not produce ovulation. Bilateral destruction of the facial nerve did not prevent the normal ovulatory response to copulation. The results seem to exclude the facial nerve from consideration as a pathway for impulses from the central nervous system to the hypophysis. The authors are inclined to believe that fibers of the infundibular stalk serve as the functional connection between the brain and the anterior lobe of the hypophysis. PALMER, Philadelphia.

CERTAIN PHYLOGENETIC ANATOMICAL RELATIONS OF LOCALIZING SIGNIFICANCE FOR THE MAMMALIAN CENTRAL NERVOUS SYSTEM. RUSSELL T. WOODBURNE, J. Comp. Neurol. **71**:215 (Oct.) 1939.

Using brains of Petromyzon, Amblystoma, Necturus and the frog, turtle, garter snake and rat, Woodburne shows that with respect to general arrangement sensory and motor cortical localization patterns are predetermined in submammalian forms before differentiated cortex appears. He presents evidence for (1) specificity of pattern in the afferent centers of the spinal cord and of the brain stem and (2) establishment of a localization pattern in primary and in cortical efferent centers. ADDISON, Philadelphia.

STUDIES ON THE DIENCEPHALON OF THE VIRGINIA OPOSSUM: I. THE NUCLEAR PATTERN IN THE ADULT. DAVID BODIAN, J. Comp. Neurol. **71**:259 (Oct.) 1939.

Bodian describes the nuclear masses in the diencephalon of the opossum in series which were cut in three planes and stained for cells, myelin and fibers. Fifty-seven nuclei are described in detail. The diencephalic pattern of the opossum is remarkable not only for its primitive features but also for the possession of

most of the typical features of higher mammalian brains. No outstanding specializations were recognized in the opossum. The diencephalon resembles most closely that of the rat, Tupaia and the armadillo.

FRASER, Philadelphia.

HISTOGENESIS OF THE MONOPOLAR NEUROBLAST AND THE VENTRAL LONGITUDINAL PATH IN THE ALBINO RAT. A. W. ANGULO Y GONZÁLEZ, J. Comp. Neurol. **71**:325 (Oct.) 1939.

Angulo studied 2,765 rat fetuses, ranging in age from 10 days to the end of gestation, 22 days. At critical stages, the litters were obtained at two-hour intervals; otherwise, every eight hours. The central nervous system was prepared by silver impregnation or the toluidine blue stain. The study begins with fetuses 1.5 mm. long and 263 hours old. At this stage the neural tube was well formed, but the most extreme cephalic and caudal ends were still open. The walls of the neural tube were very thin and the vesicles relatively large. In the cervical region migration of the cells to form spinal ganglia was progressing. Angulo describes the early histogenetic changes of the nerve cell which lead to formation of the monopolar neuroblast and recognizes five stages—early apolar, early bipolar, late bipolar, late apolar and monopolar. He believes that the early processes of the nerve cell have only the function of migration and that the late processes serve for conduction of stimuli.

In fetuses 2.0 mm. long and 264 hours old, bipolar, apolar and monopolar cells were recognized, and fibrillation had occurred. Six rhombic grooves were identified throughout the 1.5 to the 5.5 mm. stages. The ventral longitudinal pathway arose from widely separated centers located mainly in the midbrain. At the 3.4 mm. stage the nucleus interstitialis of Cajal was identified. At the 4.0 mm. stage the nucleus of the posterior commissure was recognized. At least two types of neurons formed this center. At this time the fibers of the ventral longitudinal path had reached the medulla. At the 5.5 mm. stage this path was well established in the cervical portion of the cord and received fibers from four centers—the inferomedial nucleus, the interstitial nucleus, the posterior commissural nucleus and the tectospinal nucleus. Along its caudal course the fibers of the ventral longitudinal path gave off branches which crossed in the floor plate and entered into synaptic relation with the respective motor centers of the opposite side. In later stages and in the adult, this ventral commissure was formed by fibers of heterogeneous origin and was present at the level of each motor cranial nucleus and throughout the spinal cord.

ADDISON, Philadelphia.

THE DEVELOPMENT AND STRUCTURE OF THE PRETECTAL CELL MASSES IN THE CHICK. HARTWIG KUHLENBECK, J. Comp. Neurol. **71**:361 (Oct.) 1939.

Kuhlenbeck studied serial sections of the brains of the chick from the 87 hour incubation stage until hatching. Most of the pretectal nuclei were recognizable by the seventh day of incubation. In a 12 day embryo the development of the definitive pretectal nuclear pattern was completed. In the final nuclear pattern there were fifteen cytoarchitectural nuclei, arranged into three groups: namely, the nucleus principalis praecommissuralis, the main tectal group and the nuclei of the posterior commissure. Associated with these nuclei were two nuclei of tectal origin, the nucleus lentiformis mesencephali and the nucleus parageniculatus tecti, and one tegmental nucleus, the nucleus interstitialis tegmentalis commissurae posterioris.

FRASER, Philadelphia.

THE BEHAVIOR OF THE NEURAL CREST IN THE FOREBRAIN REGION OF AMBLYSTOMA. ROLLO C. BAKER and GRANT O. GRAVES, J. Comp. Neurol. **71**:389 (Oct.) 1939.

Baker and Graves made wax reconstructions of the neural crest cells of a series of embryos of Amblystoma punctatum, stages 15, 19, 20, 22, 24 and 26 of

Harrison. Vital staining was also used. The neural crest differentiated from the ectoderm along the entire lateral border of the neural plate early in the medullary plate stage. At this stage the neural crest encircled the rostral end of the brain. For a short time the neural crest formed a plug of cells on the roof of the forebrain, and in the region of the anterior neuropore a mass of neural crest cells became wedged into the rostral extremity of the forebrain. No morphologic evidence was revealed which indicated that any portion of the neural crest was retained in the developing forebrain or its derivatives, such as the eye.

ADDISON, Philadelphia.

THE ORIGIN OF THE NERVE FIBERS TO THE GLOMUS AORTICUM OF THE CAT. W. HENRY HOLLINSHEAD, J. Comp. Neurol. **71**:417 (Dec.) 1939.

Hollinshead performed operations of three types on the right side in cats: (1) section of the vagus nerve below the nodose ganglion, in 7 cats; (2) removal of the superior cervical ganglion, in 3, and (3) section or avulsion of the vagus nerve above the nodose ganglion, by the cervical approach, in 6. From five to twenty-one days was allowed for degeneration, after which the tissue from both the right and the left carotid-subclavian region was prepared by the pyridine-silver technic. The nerve supply to the glomus was rich in the normal cat. Section of the vagus nerve below the nodose ganglion resulted in degeneration of the nerve plexus in the aortic body. Small unmyelinated fibers, presumably both vasomotor fibers to the blood vessels and fibers of passage, persisted. The fibers to the aortic body seemed to arise from cells in the nodose ganglion of the vagus nerve and were presumably sensory.

ADDISON, Philadelphia.

THE RELATIVE VASCULARITY OF SUBCORTICAL GANGLIA OF THE CAT'S BRAIN; THE PUTAMEN, GLOBUS PALLIDUS, SUBSTANTIA NIGRA, RED NUCLEUS, AND GENICULATE BODIES. HELOISE BEEKMAN HOUGH and HAROLD G. WOLFF, J. Comp. Neurol. **71**:427 (Dec.) 1939.

Hough and Wolff measured the capillary length per cubic millimeter in sections of the putamen, globus pallidus, substantia nigra, red nucleus and geniculate bodies of 6 cats given injections of berlin blue. In sections of tissue from similar regions prepared for Nissl substance the number of cell bodies and the area of the perikaryon were determined. The putamen was more vascular and had more cells than the globus pallidus or the substantia nigra. The reticular zone of the substantia nigra had about the same vascularity as the globus pallidus, but it had nearly twice as many cells per cubic millimeter. The degrees of vascularity of the medial and the lateral geniculate body were approximately the same. Of the nuclei studied, the red nucleus had the fewest cells (95) per cubic millimeter; yet the degrees of vascularity and the average sectioned area of nerve cell bodies in this nucleus were high, and the amount of neuropil was large. Vascularity of the subcortical structures was related to the total surface area of both cell bodies and neuropil.

FRASER, Philadelphia.

OBSERVATIONS ON THE CHICK GASSERIAN GANGLION WITH SPECIAL REFERENCE TO THE BIPOLAR NEURONS. R. C. TRUEX, J. Comp. Neurol. **71**:473 (Dec.) 1939.

Truex studied the gasserian ganglia of 7 normal chickens, ranging in age from 2 months to 5 years, by the strong protein silver method. The dominant cell type was unipolar, but about 2 per cent of the cells were bipolar. No typical multipolar cells were identified. Atypical ganglion cells and degenerative phenomena were recognized in the older birds. The most common degenerative feature was the formation of short angular processes from the cell surface. Continued degeneration of the cyton was accompanied by the appearance of many phagocytic cells. Atypical ganglion cells were also seen in older birds. Truex believes that

the unipolar cell is formed from gradual protrusion and elongation of the cytoplasm in the region between and at the site of attachment of the two approximating processes. The involved cytoplasm marks the region of the future axon hillock, and is itself converted into the undivided portion of the unipolar process. The gasserian ganglion of birds differs from that of man in the small amount of intraganglionic connective tissue supporting the nerve element, the arrangement of the ganglion cells into separate groups of varying numbers, the poorly developed cell capsules and the presence of bipolar and binucleated neurons.

FRASER, Philadelphia.

NERVE ENDINGS IN THE URINARY BLADDER. ORTHELLO R. LANGWORTHY and EDWARD L. MURPHY, J. Comp. Neurol. **71**:487 (Dec.) 1939.

Langworthy and Murphy investigated the nerve endings at the base of the bladder, where the trigon is found in man, by injecting methylthionine chloride U. S. P. (methylene blue) into the descending portion of the thoracic aorta in cats. Air was introduced into the bladder through the urethra and changed from time to time. The bladder was then fixed in a solution of ammonium molybdate and cleared in glycerin. Section of different nerves was performed at varying lengths of time before the staining. The position and form of the vascular plexus were determined by injecting india ink and clearing.

At the base of the bladder the large nerves and ganglia lie just beneath the peritoneum. Other groups of ganglion cells are scattered along the course of the nerve trunks. In the subperitoneal layer there are a distinctive plexus of medullated and a fine network of nonmedullated fibers. The unmyelinated nerves, which lie between the muscular layers, terminate in groups of end bulbs on the muscle fibers and in pendants of terminal bulbs which lie parallel to the fibers. Myelinated fibers form more complicated terminations on the muscle layer. These are believed to be stretch receptors. Other myelinated fibers terminate between the muscle layers, sometimes in encapsulated endings and sometimes in showers of fibrils and bulbs. After section of the sacral roots distal to the spinal ganglia the sensory component had degenerated almost completely at the end of a week. The sympathetic motor endings to the blood vessels were swollen at that time, but did not completely degenerate until toward the end of the fourth week. After bilateral section of the postganglionic sympathetic fibers the bladder was small. Fibers which end in the submucosa of the ureters and urethra degenerate in large part after sympathectomy. Sympathetic fibers innervate the muscle of the ureters and its continuation into Bell's muscles and the crista of the urethra. They also supply the majority of the fibers innervating the blood vessels. Most of the sensory nerves which form a plexus in the submucosa and mucosa at the base of the bladder belong to the sympathetic system; those over the dome, to the parasympathetic system.

FRASER, Philadelphia.

THE TELENCEPHALON OF TUPINAMBIS NIGROPUNCTATUS: III. AMYGDALA. ALICE OSBORNE CURWEN, J. Comp. Neurol. **71**:613 (Dec.) 1939.

In Tupinambis, a South American lizard, the amygdala surrounds the end of the tractus corticoarchistriaticus, and is known as the nucleus occipitobasalis or the nucleus sphaericus. Curwen recognizes eight nuclei in the amygdala and states that the connections of the different groups are probably visceral, olfactory and somatic. Homologies are indicated between the amygdala of Tupinambis and the amygdala complex of other reptiles and the lower mammals.

FRASER, Philadelphia.

AXON HILLOCKS OF MULTIPOLAR NEURONS OF THE CAT. Q. B. DEMARSH, J. Comp. Neurol. **71**:637 (Dec.) 1939.

DeMarsh studied pieces of the anterior central gyrus and of the lumbar portion of the spinal cord of 4 healthy adult cats which had been sectioned and stained

for Nissl substance. Each nerve cell was studied in its entirety. True axon hillocks were frequently absent in the large spinal and in the large cortical motor cells. When the axon hillock was present, it contained chromophil substance in the majority of cases. The axon hillock varied greatly in size. Of over 200 small cells of the ventral spinal gray matter, only 63 showed a hillock and only 2 entirely lacked chromophil substance.

ADDISON, Philadelphia.

SUBSTITUTION OF LIMBS FOR BRACHIAL SOMITES. S. R. DETWILER and B. L. MACLEAN, J. Exper. Zoöl. **83**:445 (April) 1940.

The brachial somites (3, 4 and 5) of Amblystoma embryos (stage 25 to 27) were replaced on one side by a limb rudiment from a donor of the same age. In some embryos the host limb rudiment of the same side was removed, and in others it was left intact. Single limbs, typically smaller than those in the orthotopic position, developed and became supplied by a variable number of nerves, usually by one or two. The number of rootlets from the spinal cord also varied, but there was a close correspondence between the number of nerves and the number of spinal ganglia present. The presence of two limbs had no added stimulating effect on nerve outgrowth. The number of nerves which developed, therefore, seemed to have no relation to the position, size and morphologic relation of the limb.

In many cases the position of the spinal ganglia varied from the normal to one adjacent to the base of the limb. There was evidence that the shift in position of the ganglia was not brought about mechanically; it is suggested, therefore, that the displacement is evidence of an "attractive" influence exerted on the spinal ganglia by the grafted limb. Hyperplastic responses of the cord to the presence of the proliferating limb rudiment were not found.

WYMAN, Boston.

THE DISTRIBUTION OF COMMISSURAL FIBRES IN THE CORPUS CALLOSUM IN THE MACAQUE MONKEY. S. SUNDERLAND, J. Neurol. & Psychiat. **3**:9 (Jan.) 1940.

By means of cortical lesions produced in macaque monkeys by local devascularization, Sunderland was able to outline the distribution in the corpus callosum of the commissural fibers undergoing Marchi degeneration as follows: Callosal fibers from the frontal lobe occupy approximately the genu and the anterior third of the body of the corpus callosum, with preponderance of fibers from the premotor area. The occipital fibers occupy the splenium and the posterior third of the body, the majority arising from the peristriate areas, or areas 18 and 19, rather than from the striate area, or area 17. Some of the occipital fibers course through the septum pellucidum. The fibers from the parietal and temporal lobes occupy the posterior two thirds of the body of the corpus callosum, the temporal fibers being situated more anteriorly. The commissural fibers from the temporal cortex also cross by way of the anterior commissure. This localization in the corpus callosum is, however, of a general type, since the fibers from some cortical areas are diffusely spread and there is also overlapping of fibers from different areas. The parietal cortex contributes relatively the greatest number of commissural fibers, followed by the frontal, the temporal and the occipital lobe, in that order.

MALAMUD, Ann Arbor, Mich.

ATROPHY OF THE THALAMUS IN A CASE OF ACQUIRED HEMIPLEGIA ASSOCIATED WITH DIFFUSE PORENCEPHALY AND SCLEROSIS OF THE LEFT CEREBRAL HEMISPHERE. W. E. LEGROS CLARK and D. S. RUSSELL, J. Neurol. & Psychiat. **3**:123 (April) 1940.

A girl aged 13 had an acute illness characterized by initial symptoms of vomiting, convulsions on the right side, unconsciousness and fever, followed by complete right hemiplegia, which was at first flaccid and later spastic. The spinal fluid

showed moderate pleocytosis, in which lymphocytes predominated. After a brief and partial remission, during which the residuals of the hemiplegia nevertheless persisted, there was a relapse, with attacks of coma and convulsions on the right side terminating in status epilepticus; death occurred about five years after the onset of the illness. Pathologically, there were atrophy and porencephaly of almost the entire left cerebral cortex, accompanied by advanced demyelination and gliosis of the white matter of that hemisphere. The distribution of the atrophy corresponded to the vascular territory supplied by the left middle cerebral artery and extended only to a limited degree into the territories of supply of the anterior and the posterior cerebral artery, largely sparing the cingulate gyrus, the visual striate area, the hippocampal region and a small part of the central gyri. There were also descending degeneration of the pyramidal tract and mild atrophy of the contralateral cerebellar hemisphere, but no involvement of the corpus striatum and the globus pallidus. The most striking feature was the atrophy of the left optic thalamus, consisting of almost complete degeneration of its anterior, ventral, lateral and medial nuclei, and of the pulvinar, the medial geniculate body and the reticular nucleus. The changes suggested that the parts of the thalamus involved are concerned with the projection of impulses to definite parts of the cerebral cortex, an assumption which is largely corrobrated by studies of experimental decortication. Thus, the few persistent cells in the anterior and the ventral nucleus of the thalamus were probably related to the intact parts of the cingulate and the central gyrus, respectively. The only parts of the thalamus entirely spared were the lateral geniculate body, the central median nucleus and a narrow subependymal zone of small cells. The sparing of the lateral geniculate body is probably related to the intactness of the area striata. The central median nucleus and the subependymal zone are apparently the only parts of the thalamus which do not project on to the cortex. The connections of the central median nucleus are still obscure, and the belief that it may have connections with the insular cortex, the corpus striatum or the pallidum is not borne out by the observations in this case. The authors suggest that this nucleus may represent intralaminar nuclear elements present in the thalamus of lower mammals. The existence of thalamostriatal connections is doubtful. The atrophy of the thalamus in this case may be attributed to interruption by the cortical destruction of the axonal processes, rather than to transneuronal atrophy due to interruption of descending corticothalamic fibers or to direct vascular disturbance. The etiologic factor in the acquired hemiplegia in this case remains undetermined but, as in similar cases in the literature, may be some type of encephalitis.

MALAMUD, Ann Arbor, Mich.

ONTOGENIC DEVELOPMENT OF THE CENTERS OF SPEECH. J. ARANOVICH, Rev. neurol. de Buenos Aires **4**:3, 1939.

This is a study of the gross and microscopic changes in the speech area, from fetal to adult life. The anatomic centers of speech develop during the second half of fetal life. The fissure of Rolando appears at the fetal age of 4½ months, forming the opercula, and the fissure of Sylvius appears at the same time. The first temporal sulcus forms at 5 months. The development of the inferior frontal sulcus, at 6½ months, outlines the third frontal convolution. The deep temporal convolution appears after the seventh month of gestation.

The maturation of the centers of speech during infantile life is characterized chiefly by the development of the foot of the left third frontal convolution and of the upper internal surface of the temporal lobe. The former convolution closes the lips of the ascending branch of the fissure of Sylvius. The latter convolution gives rise to the planum parinsulare. The maturation of the histologic structure of the region also goes through various stages, which are described. The chief source of increase during the first year of life is not proliferation of cells but chiefly myelination and the formation of other intercellular structures.

PUTNAM, New York.

Physiology and Biochemistry

THE MECHANISM OF COCARBOXYLASE ACTION. K. G. STERN and J. L. MELNICK, J. Biol. Chem. **131**:597, 1939.

Stern and Melnick find that the mechanism by which cocarboxylase (thiamine pyrophosphate) exerts its catalytic activity is probably by reversible reduction and oxidation of the double bond adjoining the quaternary nitrogen in the thiazole nucleus. Dihydrothiamine has no antineuritic activity in pigeons, while dihydrococarboxylase is highly active. Pyruvic acid is apparently not decarboxylated by combination with cocarboxylase to form a catalytically active substituted amino acid.

PAGE, Indianapolis.

DEFICIENCY OF VITAMIN B_1 IN MAN AS DETERMINED BY THE BLOOD COCARBOXYLASE. R. GOODHART and H. M. SINCLAIR, J. Biol. Chem. **132**:11, 1940.

Vitamin B_1 acts in the body as a catalyst, necessary for degradation of pyruvate, only after it has been converted into its diphosphate ester, cocarboxylase. It circulates in plasma in the free, unphosphorylated form and diffuses readily into the tissue fluid, cerebrospinal fluid, urine and cells of the body. Phosphorylation of the vitamin, with formation of cocarboxylase, occurs inside the cells.

Goodhart and Sinclair found that the amount of cocarboxylase in the blood varies directly with the amount of total vitamin B_1 and also with the degree of saturation of the tissues with the vitamin. The only exceptions occur in patients in whom the blood cell count is greatly increased (polycythemia vera or myeloid leukemia) and in patients who have recently received intensive vitamin B_1 therapy. In most cases determination of the amount of cocarboxylase provides a rapid and reliable method of estimating the degree of saturation of the tissues with the vitamin.

Deficiency of vitamin B_1 is associated anemia, subacute combined degeneration of the cord and some psychiatric disorders. Diminished gastric acidity tends to be associated with deficiency of vitamin B_1.

PAGE, Indianapolis.

ON THE ISOLATION OF A GLUCOSE-CONTAINING CEREBROSIDE FROM SPLEEN IN A CASE OF GAUCHER'S DISEASE. N. HALLIDAY, H. J. DEUEL JR., L. J. TRAGERMAN and W. E. WARD, J. Biol. Chem. **132**:171, 1940.

Halliday, Deuel, Tragerman and Ward have demonstrated that, unlike the cerebroside in normal brain, the cerebroside extracted from the spleen in a case of Gaucher's disease contained dextrose rather than galactose. In other respects it resembled kerasin. They suggest that the dextrose-containing cerebroside is the result of an anomaly in carbohydrate metabolism rather than a characteristic of Gaucher's disease. In at least 1 case of Gaucher's disease galactose has been identified as the carbohydrate component. Possibly, instances in which dextrose replaces galactose in the cerebrosides of the brain may eventually be observed.

PAGE, Indianapolis.

THE GLUTAMIC ACID OF MALIGNANT TUMORS. SAMUEL GRAFF, D. RITTENBERG and G. L. FOSTER, J. Biol. Chem. **133**:745, 1940.

The claim of Kögl and Erxleben that malignant tumors contain the unnatural *d* (—)-glutamic acid was not confirmed. By using the isotope dilution method, 6 specimens of malignant tissues were found to contain *l* (+)-glutamic acid in amounts ranging from 6.7 to 8.7 per cent of the total nitrogen. The other isomer, if present at all, could not have been more than 1.0 per cent of the total glutamic acid.

PAGE, Indianapolis.

CLINICAL STUDY OF HYPNOTICS: EFFECT ON GROSS SLEEP MOVEMENTS, LENGTH OF SLEEP, BLOOD PRESSURE, RESPIRATORY RATE AND PULSE RATE. F. MEYERS, E. D. COOK and R. C. PAGE, New York State J. Med. **40**:12 (Jan. 1) 1940.

Meyers and his co-workers determined the influence of therapeutic doses of hypnotics on the length of sleep, the time of its onset, the number of gross movements during sleep and changes in pulse rate, respiratory rate and blood pressure. Subjects for the experiments were patients who were free from pain and were not having treatment which might have influenced their sleep. None of these patients received opiates or sedatives as part of their daytime treatment. During the day the subjects received their usual routine care in the ward, but from 9 p. m. to 8 a. m., and longer when necessary, they were kept in a separate room and were under the constant observation of a nurse especially trained for the study. The two beds used for the experiment were attached to actographs. The drugs used were a placebo, n-tolylbutylethylbarbital, neonal, a urea derivative, pentobarbital sodium and sodium amytal. Various doses within the therapeutic range were administered. Each of these drugs was pressed into tablets, all having a similar appearance so that the subjects would not know what medication they were receiving. Twelve patients were studied for a total of two hundred and nineteen nights of observation. Each subject remained in the sleep room for a minimum of fourteen days and a maximum of twenty-six days. The placebos and the hypnotics were not given in any definite order, but each patient received the placebo at least four times during the course of study. The authors found that the time of onset of sleep was not more rapid after the use of any one hypnotic. The average length of sleep was increased about twenty minutes. The sleep pattern, as measured by the number of gross movements made during sleep, was not changed, except in 4 cases of congestive heart failure. In these instances the hypnotics increased the number of movements during sleep. The pulse rate, respiratory rate and blood pressure in the 12 subjects with normal cardiovascular mechanisms were consistently depressed by the hypnotics, while the 4 patients with congestive heart failure showed but little change.

J. A. M. A.

VASCULAR CHANGES AFFECTING THE TRANSMISSION OF NERVOUS IMPULSES. EDITH BÜLBRING and J. H. BURN, J. Physiol. **97**:250, 1939.

In an analysis of the fact that sympathetic stimulation improves the function of fatigued skeletal muscle, the authors studied the effect of such stimulation on transmission of nerve impulses in the fibers of the sciatic nerve in dogs. They also studied the effect of administering epinephrine and other vasoconstrictor drugs. In perfused preparations, after the conductivity had been lessened by prolonged perfusion, they observed that any stimulus tending to cause vasoconstriction improved the conductivity of the sciatic fibers. It was therefore possible to demonstrate an increase in the height of contraction of fatigued skeletal muscle by means of sympathetic stimulation or the administration of vasoconstrictor drugs which affected only the environment of the sciatic nerve trunk, and not the muscle itself. They conclude that sympathetic stimulation improves the function of fatigued skeletal muscle by three mechanisms: (1) by increase in the conductivity of the nerve trunk; (2) by improvement in neuromuscular transmission, and (3) by direct action on the muscle substance.

THOMAS, Philadelphia.

CALCIUM AND SYNAPTIC TRANSMISSION IN A SYMPATHETIC GANGLION. A. M. HARVEY and F. C. MACINTOSH, J. Physiol. **97**:408, 1940.

Harvey and MacIntosh studied the effects of changes in ionic equilibrium on synaptic transmission and the activity of ganglion cells in the perfused superior cervical ganglion of the cat. The omission of calcium from the perfusion fluid, other cations being present in normal concentrations, has the following effects: *(a)* the ganglion cells discharge spontaneously; *(b)* synaptic transmission fails, owing to the failure of preganglionic impulses to liberate acetylcholine; *(c)* the ganglion

cells are sensitized to both the stimulating and the paralyzing action of injections of potassium chloride, and *(d)* the response of the ganglion cells to injection of acetylcholine is diminished. These results are not obtained on perfusion with isotonic solution of sodium chloride or with solutions containing an excess of potassium, but a normal concentration of calcium. THOMAS, Philadelphia.

Neuropathology

ORIGIN OF PERINEURAL FIBROBLASTOMA. I. M. TARLOV, Am. J. Path. **16**:33 (Jan.) 1940.

Tarlov believes that he is the first to demonstrate by direct staining methods in 2 perineural fibroblastomas of the vagus nerve roots that the type cell of this tumor is not the Schwann cell. Dockrill's modification of Hortega's silver impregnation technic was the method employed for the demonstration of Schwann cells. Direct staining revealed normal and proliferating Schwann cells, which excluded the Schwann cell as the type cell of the encapsulated tumor of the peripheral nerves. The type cell of these tumors presented morphologic characteristics of the fibroblast. The term perineural fibroblastoma should be retained for encapsulated tumors of peripheral nerves, although it must be realized that they may arise from endoneurium, as in the case of the tumors of the vagus nerve roots. Although the occurrence of nerve fibers within an encapsulated tumor of a peripheral nerve is usually characteristic of multiple neurofibromatosis, an occasional nerve fiber may occur within a solitary perineural fibroblastoma. J. A. M. A.

PRIMARY TUMORS OF THE OPTIC NERVE (A PHENOMENON OF RECKLINGHAUSEN'S DISEASE). F. A. DAVIS, Arch. Ophth. **23**:735 (April); 957 (May) 1940.

Davis reaches the following conclusions concerning tumors of the optic nerve:

"So-called primary tumors of the optic nerve usually appear as one of two types, namely, gliomas and endotheliomas, the former being much the more common. Endotheliomas resemble those found in the brain, known as meningiomas or meningeal fibroblastomas. They arise from the dura or arachnoid sheath of the nerve or at times by extension from similar growths within the cranial cavity.

"This study indicates that glial tumors start with an abnormal proliferation of the normal adult types of neuroglia of the nerve stem. After varying periods of growth, the abnormal neoplastic neuroglial cells penetrate the pia, with the formation of a gliomatous tumor in the sheath. Proliferation of the mesothelial cells of the arachnoid follows the glial penetration of the pia, with the formation of a tumor-like mass in this portion of the nerve sheath. Later, intermingling of the proliferated cells from these two areas produces a complex histologic structure, the precise nature of which is difficult to interpret unless earlier stages of the growth have been studied.

"Since these growths exhibit all the characteristics of true tumors, they should be designated as gliomas. Such terms as gliomatosis [and] astrocytosis should be used merely as descriptive terms for the earliest phase of their development. Complete histogenesis of the neoplastic cells has not been determined. Such types as spongioblastoma, spongioneuroblastoma, astrocytoma and oligodendrocytoma have been reported.

"The outstanding feature of the neoplastic cells was excessive fiber formation within as well as without the nerve stem. This, together with the general character of the cells as revealed by special staining, indicates that predominant cell types were astrocytes, so that these tumors are designated astrocytomas.

"The cause of Recklinghausen's disease and related lesions is not known. Pathologists are in disagreement concerning the nature of the tumors which accompany the disease. The lesions which make up this syndrome are more widespread than at first believed. One group of pathologists maintains that tumors

of the peripheral nerves arise from some defect in the sheath of Schwann cells, a neuroectodermal derivative, while others assert that they arise from the fibrous elements of the nerves.

"Studies of del Rio Hortega, which are endorsed by Penfield, indicate that the oligodendroglia of the central nervous system, which includes the optic nerve, is homologous with the Schwann cells of the peripheral nervous system. A similar function of the two cell elements, namely, maintenance of the myelin sheath of the nerve, is therefore probable. A defect of these homologous structures has been suggested, therefore, by del Rio Hortega as a common source of origin of tumors of the optic nerve and tumors of the peripheral nerves.

"Attempts to find some common background for all the tumors which make up the Recklinghausen syndrome, as now known, is complicated by the great dissimilarity in structure of some of the tumors. This suggests that the primary lesion in this complex disease must be sought in some degenerative change which primarily affects the nerve substance itself, while the tumors which follow may be secondary growths in the various supportive elements.

"That tumors of the optic nerve probably belong to a system disease, as originally suggested by Emanuel, is borne out by the simultaneous appearance of multiple lesions in the central and the peripheral nervous system, by the fact that the tumors are bilateral at times and, further, by the fact that multiple involvement of the nerve has been reported. The slow rate of growth and the relatively benign nature of the tumors are characteristic of other lesions associated with this syndrome.

"This study and review of the literature led [Davis] to conclude that tumors of the optic nerve are in many if not most instances but a part of a more widely disseminated lesion of the peripheral and central nervous systems, commonly referred to as neurofibromatosis or Recklinghausen's disease.

"The term 'neurofibromatosis' or 'neurofibroma' as applied to tumors of the optic nerve should be abandoned, for they are usually gliomas or endotheliomas."

SPAETH, Philadelphia.

MULTIPLE MENINGIOMA WITH SARCOMATOUS TRANSITION IN ONE NODULE. C. P. LARSON, C. M. STROUD and F. K. STROUD, Arch. Path. **28**:861 (Dec.) 1939.

A case of multiple leptomeningioma is reported, an unusual feature being a sarcomatous change in the largest of the growths. This growth had invaded both the calvarium and the underlying parenchyma of the brain, with gross destruction of the entire right frontal lobe. There was a marked increase in intracranial pressure. Many instances of multiple meningioma were found in the literature, but in only 1 case was the presence of cells resembling those of sarcoma mentioned. A single tumor, somewhat similar to that described in this paper, was reported by Globus and was classified as leptomeningioma with a tendency toward sarcomatous transition.

WINKELMAN, Philadelphia.

FORMS OF GROWTH IN GLIOMAS AND THEIR SIGNIFICANCE. H. J. SCHERER, Brain **63**:1 (March) 1940.

Scherer studied at necropsy the mode of growth in 120 cases of glioma. Pyroxylin sections including the whole tumor with surrounding tissues, from one end of the glioma to the other, were utilized in the study. This method is indispensable, as the majority of gliomas are more extensive than their macroscopic aspect might lead one to suppose. All gliomas, except ependymoma, show an infiltrative type of growth, although in widely differing degrees, by no means corresponding to the more or less "malignant" aspect of the glioma cells. Cerebral astrocytomas are the most invasive of all cerebral tumors, while glioblastomas include a considerable percentage of fairly well defined neoplasms with a narrow zone of growth. The cytologic tumor entities include gliomas of quite different

types of growth, proving that cytologic features and histogenesis are insufficient to characterize the biologic behavior of a given glioma. Only about 30 per cent of tumors are relatively circumscribed; their real extent exceeds but moderately their macroscopically visible limits. This group includes oligodendrogliomas, many cerebellar astrocytomas and certain medulloblastomas. Factors underlying this surgically rather favorable mode of growth are (1) a narrow, compact zone of growth, (2) a halting of the tumor at certain preexisting structures, especially the cortex, and (3) degenerative processes at the edge. Tumors of the hippocampal region and the septum lucidum grow frequently in the form of round, expansive masses in the ventricular cavity. About 60 per cent of gliomas have a more diffuse character, with a widespread zone of growth considerably exceeding the macroscopically visible "tumor" and involving more than one lobe. Nearly 35 per cent show what is probably a secondary diffuse growth, while 25 per cent must be considered as primarily diffuse neoplastic processes which do not form a circumscribed tumor. All cerebral astrocytomas belong to this group. In the common case of malignant dedifferentiation of an astrocytoma into a glioblastoma, often the glioblastoma alone is visible as a macroscopic "tumor," surrounded by a large astrocytomatous zone, the true character of which is discovered only by microscopic examination. About 10 per cent of gliomas show a primarily multicentric type of growth, and in half these cases this multicentricity is visible only on complete microscopic study. The macroscopic examination shows only one main tumor. Infiltration and destruction by growth are by no means necessarily associated in gliomas. Long-continued preservation of nerve cells and fibers in the midst of tumor tissue is not specific for astrocytomas (although most constant for this form), but occurs also in glioblastomas. J. A. M. A.

ANTIBODIES TO BRAIN AND THEIR RELATION TO DEMYELINIZATION. L. C. KOLB and B. BOLTON, J. Neurol. & Psychiat. **3**:111 (April) 1940.

Intraperitoneal injections of emulsions of rat brain in rabbits over a period of three months produced specific antibodies to brain in the rabbit serum. This serum, however, when injected in rats, failed to cause lesions in the brain. This disproves the suggestions made by other authors that the demyelination observed in some animals after injection of emulsions of the brain or that the demyelinating diseases in general are due to the development of autogenous antibodies to brain or to some cerebrotoxin. MALAMUD, Ann Arbor, Mich.

THE CENTRAL NERVOUS SYSTEM IN CONGENITAL ABSENCE OF ONE LEG. E. W. WALLS, Lancet **1**:123 (Jan. 20) 1940.

Knowledge of the neuropathologic changes occurring in the neuraxis as a result of congenital abnormalities of the extremities or of amputation is incomplete. In disagreement with Taft, who stated that no change in the spinal cord occurs after amputation, Walls presents data which support the stand of Campbell, namely, that "in long-standing cases the predominant change is a homolateral atrophy, represented by a general reduction in volume of white and grey matter alike, and involving those particular segments of the cord which receive and give off the sensory and motor nerves which originally supplied the skin and muscles of the amputated member." The posterolateral cells are more liable to atrophy.

Walls studied brain and spinal cord of a woman aged 75, who died of pneumonia. Her congenital deformities consisted of absence of the left leg below the knee and complete absence of both hands, only rudimentary thumbs being recognizable. The greatest asymmetry was observed in the sacral segment of the cord, the left side being smaller than the right in all components. The tractus gracilis higher in the cord was small. The brain stem and the right side of the cortex were normal.

Three theories concerning the pathogenesis of congenital abnormalities are suggested: (1) There may be either faulty development of certain cells in the nervous system or, possibly, hypertrophy of a group of cells; (2) amniotic bands may amputate normally developing limbs, and (3) the primary anlage may have a "faulty quality."

KRINSKY, New London, Conn.

SUPERIOR ALTERNATING HEMIPLEGIA. V. DIMITRI, Rev. de neurol. de Buenos Aires **4**:83, 1939.

A man aged 74 who was alcoholic presented a syndrome of left hemiplegia with contralateral oculomotor paralysis. The hemiplegia was of an extremely spastic type, without the Babinski sign. There were, however, no athetoid movements. A year later a second stroke occurred, with conjugate deviation of the eyes to the right and contracture in flexion of the right arm. The right leg was spastic. All deep reflexes were exaggerated on the right. At the same time the spastic paralysis of the left side was transformed into the flaccid type. The patient remained in coma and died.

Autopsy showed an old lesion of the right substantia nigra and a lesion affecting both red nuclei. There were numerous other small lesions. It is not clear where the terminal lesion lay. The pyramidal tracts were intact.

PUTNAM, New York.

HISTOLOGIC CHANGES IN THE NEIGHBORHOOD OF IMMATURE TUMORS OF THE BRAIN. G. DÖRING, Deutsche Ztschr. f. Nervenh. **149**:201, 1939.

The area about immature tumors was studied in sections stained by the Nissl, Holzer, Cajal, hematoxylin-eosin, Bielschowsky and Perdrau methods; the tumors were chiefly glioblastomas, but a few astroblastomas and medulloblastomas were available. The "infiltrative periphery" is more common than the fibrous reaction about "expensile" gliomas. Beyond the fibrous rim, when it is present, is a reaction similar to that about infiltrative growths. In the growth area are hyperplastic astrocytes, spongioblast-like cells and microglial elements. Tumor cells may be seen in abundance; small cystic areas with degenerating glioblastic cells are present. Many astrocytes are sometimes seen; these are not substrate for the tumor and do not dedifferentiate into less mature cells, but are evidence of the mobile character of the reactivity of the brain. When a degenerative reaction is seen in the astrocytes, it may be a precursor to a mesodermal reaction. These changes do not occur as markedly about medulloblastomas as about other tumors. Meningeal implants may not be surrounded by the same reactive tissue as is the parent tumor. Whether the reactive zone is gliotic or glioblastomatous must be decided in each case. Connective tissue is seen about the blood vessels, especially at the periphery of the tumor. This may be by proliferation of the intima or adventitia or by formation of knots of capillaries. These vessels are not blastomatous per se, but are a response of the brain to the needs of the tumor, and are in essence the tumor's stroma.

LOWIS, New York.

HYPOPHYSIAL TUBERCULOSIS AS CAUSE OF DEATH. W. BERBLINGER, Schweiz. med. Wchnschr. **69**:1217 (Dec. 2) 1939.

Berblinger reports the case of a woman aged 52 who injured the back of her head in a fall. Convulsions and coma set in and she died. Necropsy disclosed extensive atrophy of the entire hypophysis, the weight of which had shrunk to 0.31 Gm., leaving no distinguishable demarcation between the two lobes. Epithelioid cell tubercles with typical giant cells and caseation were found in what remained of the gland. Likewise, bilateral atrophy of the adrenal cortex, especially in the zona fasciculata, was discovered. There were subpleural calcifications in the lower lobe of the left lung and small clarified cavities in the apex, with

cicatrices in the apexes of both lungs and healed endocarditis in the aortic valves. There was almost complete absence of pubic and axillary hair. No external signs of occipital contusions were observed, nor did microscopic inspection of the brain indicate recent softening, scars or hemorrhages. Authentic proof of hypophysial tuberculosis, the author states, can be furnished only by necropsy. In the absence of this, the real cause of a patient's death may escape notice. This may account for the fact that only 21 cases have been reported. J. A. M. A.

POSTVACCINAL ENCEPHALOMYELITIS. ADELHEID LEIFEN, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:352 (Jan.) 1939.

Leifer reports the case of a girl aged 5 who died four weeks after vaccination. Three days after the vaccination persistent headaches and body pains developed. The patient then became listless and sleepy. After thirteen days vomiting began, and on the next day she refused food. She was admitted to the hospital fifteen days after the vaccination. She was somnolent and febrile and did not respond to commands or to intense stimuli. The upper limbs were rigid, and the head was turned to the left. There was opisthotonos, with forced conjugate deviation of the eyes to the left. The pupils reacted to light. The radial and periosteal reflexes were more active on the right than on the left; the abdominal reflexes were not obtained; the knee and ankle jerks were equally active on the two sides; the left plantar reflex was of the Babinski type; a mild Kernig sign was elicited on both sides; there were abnormal movements of the whole right upper limb. Lumbar puncture revealed a pressure of 300 mm. of water, with 74 cells, of which 73 were lymphocytes. There were 13,700 white cells in the blood, with 92 per cent polymorphonuclear cells. The sugar content of the spinal fluid was 66 mg. per hundred cubic centimeters. Choreiform movements in the right upper limb persisted. A facial tic appeared. The child died one month after vaccination.

Areas of demyelination and perivascular accumulations of cells were scattered throughout the brain and cord. The white substance of the cerebral hemispheres, the brain stem and the cord was involved, as well as the gray matter of the cortex, the cord and the basal ganglia. The center of the areas of involvement was always a vein. The perivascular cells were glial, mainly gitter cells and more rarely rod cells and astrocytes. Ganglion cells in the affected areas were spared. No periarterial foci were seen. The axons were relatively preserved. Leifer noted the presence of subependymal foci near the lateral ventricles and subpial lesions in the cord. There was rather marked disturbance in the cytoarchitectonics of the cortex in the region of the cornu ammonis and in the occipital area. There was considerable dropping out of ganglion cells. These changes were similar to those described by Spielmeyer in cases of convulsions associated with pertussis, and have been considered as due to vasomotor spasms.

SAVITSKY, New York.

CHANGES IN THE PYRAMIDAL MOTOR SYSTEM IN HUNTINGTON'S CHOREA. M. SCHOPE, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:679 (Feb.) 1940.

A man, who died at the age of 55, had had chronic progressive chorea since the age of 36. He had been hospitalized for five years before he died. He had paranoid ideas. In addition to the choreiform movements, he presented widening of the right pupil, which reacted more sluggishly to light than did the left, clouding of the right lens and mild weakness of the left facial nerve in all three branches. There was no sign of involvement of the pyramidal tracts or evidence of impairment of sensation. The family history was irrelevant.

There was mild diffuse atrophy of the brain, with some subarachnoid bleeding over the left hemisphere. A coronal section showed internal hydrocephalus. Grossly, the nucleus caudatus and the putamen looked smaller than normal. The small cells of the striatum were severely altered; hardly an intact cell of this type remained. The large cells of the globus pallidus were also involved. The

substantia nigra, likewise, showed degenerating cells. The red nucleus and corpus subthalamicum were relatively intact. The cells in the hypothalamic nuclei showed significant degenerative changes. Proliferating glia cells were seen throughout the precentral area. The Betz cells in the fifth layer showed the histologic picture of primary irritation. Similar changes were seen in the upper part of the hypoglossal and the Roller nucleus and in the anterior horns of the upper cervical region of the cord. The cells of the facial nucleus were pyknotic and degenerated, which accounted for the paralysis of the face. There was no demyelination of the pyramidal tracts. The cell changes in the precentral area indicate a relatively acute process, in contrast to the chronic degenerative process in the striatum. The absence of pyramidal tract signs and demyelination of the pyramidal tracts makes it impossible to use this case in support of the theory of Wilson that lesions of the precentral area are necessary for the appearance of chorea. The changes in the Betz cells described in this case were not necessarily of short duration. Gagel showed that these retrograde cell changes persist for a number of years after section of the posterior roots.

SAVITSKY, New York.

Psychiatry and Psychopathology

THE GENETICS OF PHENYLPYRUVIC OLIGOPHRENIA. GEORGE A. JERVIS, J. Ment. Sc. **85**:719 (July) 1939.

Jervis reports on a genetic study of 200 cases of a recently recognized type of mental deficiency, phenylpyruvic oligophrenia. Fölling, in 1934, reported finding phenylpyruvic acid in the urine of 10 mentally defective patients; in 6 of these the condition was present in 2 members of the sibship. In 1935 Penrose, basing his conclusion on a study of 50 cases, offered evidence for the hypothesis of a single recessive gene substitution.

The disease is characterized by alteration in the metabolism of phenylalanine (phenylaminopropionic acid). There is strong evidence that this amino acid is not oxidized by the organism. An abnormally high amount of phenylalanine, in fact, is found in the blood. The phenylalanine is then transformed into phenylpyruvic acid, mainly by the kidney, and this acid is excreted in the urine. Clinically, the disease has a fairly well defined symptomatology. In the majority of cases anomalies of the motor system are demonstrable: increase in muscle tonus; hyperactivity of the deep reflexes; knee and ankle clonus, and hyperkinetic and dyskinetic manifestations, such as athetotic and choreatic movements and tremor. Pronounced intellectual defect is present in all cases; in the present material, two thirds of the patients were idiots and one third imbeciles.

The disease seems to fulfil the initial condition of mendelism, its biochemical characteristic constituting a biologic unit. Identification of the person possessing the character is made by an exact laboratory method, the test for phenylpyruvic acid. Thus, a clearcut distinction can be drawn between affected and nonaffected members of a family.

The author finds that his data are consistent with the quantitative requirements of the theory of monomeric recessivity, since: (*a*) the ratio of affected to normal sibs in families with normal parents, when corrected by a specific method of statistical analysis, is found to be 25 per cent; (*b*) the rate of consanguinity among the parents of affected persons is significantly higher than normal; (*c*) the distribution of the character among ascendant and collateral relatives follows the rules of monomeric recessivity. Phenylpyruvic oligophrenia, therefore, appears to illustrate clearly a type of mental deficiency determined by a single autosomal recessive gene.

The practical implications of this conclusion are obvious. Parents of children affected with phenylpyruvic oligophrenia should be discouraged from having other children. Parenthood should also be discouraged in brothers and sisters and

uncles and aunts of affected persons. Consanguineous marriages among members of families of patients should particularly be prevented. Moreover, the patients should be segregated to prevent childbearing, since the great majority reach sexual maturity.

Amaurotic idiocy is also due to faulty metabolism. The two conditions seem to be analogous. Both are characterized by faulty metabolism. In the condition described by Jervis the protein metabolism is at fault, whereas in amaurotic idiocy the fat metabolism is at fault. The author believes that in all cases of familial mental defect there is a certain kinship in the sense of a faulty metabolism. This probably plays an important role in the transmission of mental defect in general.

KASANIN, San Francisco.

PSYCHIATRIC COMPARISON OF ARTIFICIAL MENOPAUSE AND THE EFFECTS OF HYSTERECTOMY. A. J. LEWIS and J. JACKSON, J. Neurol. & Psychiat. **3**:101 (April) 1940.

By comparing the incidence of neurotic symptoms in 25 women who suffered an artificial menopause through surgical removal of both ovaries with those of 42 women in whom only hysterectomy was performed before they had reached the menopause, Lewis and Jackson attempted to determine the relative causal importance of endocrine changes and psychologic reactions. The investigations were carried out over a period of four years and consisted of recording the physiologic symptoms, such as flushings, giddiness, headaches, breathlessness, increase in weight, growth of hair, pains, disturbed sleep, changes in appetite and libido and cyclic phenomena, and psychologic symptoms, such as anxiety, depression, irritability, impairment of memory and obsessional and hypochondriacal phenomena. The two groups did not differ appreciably with regard to other factors. The frequency of neurotic symptoms was about the same in the two groups. However, in the noncastrated women there were frequently concomitant physiologic changes indicating that the menopause had subsequently supervened. In both groups, the patients who showed the most pronounced neurotic symptoms were also those who had definite physical evidence of the menopause. The findings suggested that although other factors, such as predisposition and environmental stress, must be considered, there is a significant and direct association between the psychologic reactions and the endocrine changes of the menopause.

MALAMUD, Ann Arbor, Mich.

METRAZOL THERAPY FOR CONDITIONS OTHER THAN SCHIZOPHRENIA. P. DELMAS-MARSALET, M. BERGOUIGNAN and J. LAFON, Encéphale **1**:225 (May) 1939.

On the basis of the observation of the antagonistic effects of bulbocapnine and cocaine on the brain of the dog and of diethyldiallylbarbiturate of diethylamine (somnifen) and metrazol on the brain of the rabbit, the theory of "nerve isomerism" is advanced to account for the results of convulsive therapy in nonschizophrenic psychoses. The authors believe that the psychoses represent not a cerebral "deficit" but a reversible functional arrangement—an "isomeric" state. Metrazol brings about a new "isomeric" state in two stages: rapid dissolution of nerve functions, followed by an integration which is governed by a "formative instinct." Twenty-one cases of delirium and manic-depressive psychosis are reported.

RHEINGOLD, Chicago.

Meninges and Blood Vessels

INFLUENZAL MENINGITIS. N. SILVERTHORNE and others, J. Pediat. **16**:456 (April) 1940.

Silverthorne and his associates made a comparative study of influenzal meningitis over a period of twenty years. Of 70 patients treated from 1919 to 1929,

69 died, a mortality of 98 per cent. From 1930 to 1939, 65 patients were treated with anti-influenzal serums and 50 of these died, a mortality of 76 per cent. "Head cold," occurring from two days to one month prior to the onset of meningeal signs, were present in 31 of the 65 patients. Fever, vomiting, drowsiness and irritability were present in the majority. "Soreness of the neck" or "stiffness of the neck" on attempted movement was complained of by many children. There was little difference in the mortality rate for patients treated with anti-influenzal horse serum intravenously and anti-influenzal horse serum and human serum (complement) intrathecally and the mortality rate for those treated with anti-influenzal horse serum intravenously and bactericidal guinea pig serum intrathecally. During the last four years the authors studied 32 strains of Haemophilus influenzae obtained from the cerebrospinal fluid of their patients. Thirty-one of the strains examined fell into type B. Twenty-eight of the 32 strains were found to have some degree of virulence and 4 strains no virulence in mice. From the observations it appears that cerebrospinal fluid strains in cases of influenzal meningitis are, in the main, a homogeneous series, with a few exceptions: One strain did not produce indole; 1 strain was not type B, and 4 strains (3 patients from whom these strains were obtained recovered) did not possess virulence when injected with mucin into mice intraperitoneally. Because of technical difficulties in the production of guinea pig serum, the authors developed an immune anti-influenzal rabbit serum which contains mouse-protecting antibodies against a fatal infection with meningeal strains of H. influenzae. They used this serum and sulfapyridine in 1 case, with gratifying results. The combined administration of chemotherapeutic agents and immune serum mixtures is recommended rather than the use of either alone. In addition, continuous intravenous therapy and daily lumbar puncture with drainage should be carried out. In a series of experiments they found that, with the combined therapy, mouse-protecting antibodies are developed in the serum of rabbits given injections of meningeal strains of H. influenzae. J. A. M. A.

CAUSE OF REDUCTION OF SUGAR CONTENT OF CEREBROSPINAL FLUID IN MENINGITIS. E. HENDRY, Arch. Dis. Childhood **14**:307 (Dec.) 1939.

Reduction in the dextrose content of the cerebrospinal fluid is a familiar observation in all forms of meningitis, but the cause has not yet been definitely determined. From a review of the literature, it seems unlikely that lessened permeability of the choroid plexus to the passage of sugar into the cerebrospinal fluid is the cause of the reduction. The evidence points, rather, to the action either of bacteria or of leukocytes. The author devised tests to determine if there is an alteration in the permeability of the blood-brain barrier to dextrose, if the action of bacteria is the cause of the reduction or if the presence of leukocytes is responsible for the reduction. He observed that in the early stages of cerebrospinal fever a greatly increased cell count and a positive bacterial culture are almost invariably encountered. At this time the sugar content is extremely low. The patients were treated with sulfanilamide, and sterile cerebrospinal fluid was found on the second, or at the latest on the third, occasion on which lumbar puncture was performed. As at this stage of the illness the cell count is still high and the sugar content, though rising, well below normal limits, these observations suggest that meningococci are not responsible for the breakdown of dextrose. In cases of meningococcic meningitis the cell picture of the fluid changes from one almost entirely of polymorphonuclear cells to one largely of lymphocytes. In the early stages there is great reduction in the sugar content of the cerebrospinal fluid, while in the later stages, when the exudate is largely composed of lymphocytes, the sugar content approaches the normal level. In conditions such as benign lymphocytic meningitis, in which there is a purely lymphocytic exudate, there is no reduction of sugar in the spinal fluid. In 2 cases of meningitis due to Bacillus coli there was complete absence of sugar in the cerebrospinal fluid, an occurrence which might be expected as two factors are operative: a strongly glycolytic organism and a large polymorphonuclear cellular exudate. In the case of tuberculous meningitis conclusions

are not so easily drawn, but it is suggested that, as the tubercle bacillus has practically no power to break down sugar and as it is present in the cerebrospinal fluid only in small numbers, the part that it plays in reducing cerebrospinal fluid sugar need not be considered. In the early stages of the disease the cellular exudate in the spinal fluid is largely lymphocytic, and at this time the sugar content of the fluid is not greatly below normal. As the disease progresses to its fatal issue there are an increase in the number of polymorphonuclear cells and a simultaneous decrease in the sugar content. It is concluded that polymorphonuclear leukocytes possess powers of glycolysis and that their presence is the reason for a reduction of sugar in the cerebrospinal fluid in purulent meningitis and for the progressive decrease in tuberculous meningitis.

J. A. M. A.

Cerebral Haemorrhage from Rupture of a Congenital Intracerebral Aneurysm in a Child. K. Hermann and A. R. Macgregor, Brit. M. J. **1**:523 (March 30) 1940.

Hermann and Macgregor call attention to the infrequency of acute cerebral vascular catastrophes in young persons. Often, especially in cases in which the patient lives, a more exact diagnosis than this cannot be made. The authors are of the opinion that spontaneous arterial hemorrhage that is entirely intracerebral arises from rupture of an aneurysm located on one of the smaller intracerebral arterial branches. They were unable to find any record in the literature of a verified congenital intracerebral aneurysm, with or without rupture and hemorrhage. A partial explanation of this, they believe, is that aneurysms occur less frequently on the smaller arteries within the brain substance than on the larger vessels at the base; because they are so small they are harder to find, and when death occurs the minute lesion which contains clot is also surrounded by clot, thus making it difficult to see.

The authors report a case of cerebral hemorrhage from rupture of a congenital intracerebral aneurysm in a boy aged 4½ which proved fatal. The histologic changes, the relation of the aneurysm to junctions of blood vessels, the age of the patient and the demonstration of "Forbus defects" in other arteries at the base of the brain indicated that this was a congenital aneurysmal lesion.

Echols, New Orleans.

Diseases of the Spinal Cord

Acute Infectious Lesions of Intervertebral Disks. R. K. Ghormley, W. H. Bickel and D. D. Dickson, South. M. J. **33**:347 (April) 1940.

Ghormley and his colleagues discuss the occurrence of a lesion of the spine which involves principally the intervertebral disks. There is a more or less severe febrile onset, denoting a primary or secondary infectious process as the underlying cause. In the American and English literature the condition is referred to as osteomyelitis of the vertebrae. The authors have observed several cases in which roentgenographic evidence of actual osteomyelitis was so slight as to cause reasonable doubt. Sternberg described similar cases under the name of "acute spondylitis infectiosa" and drew a clearcut picture of the difference between osteomyelitis of the spine and the condition under discussion. Infectious spondylitis usually follows typhoid or paratyphoid fever (typhoid spine) and may occur as a sequela to other infectious diseases, such as undulant fever. Definite knowledge of this condition exists, but no attempt has been made to distinguish it from osteomyelitis of the vertebrae. Twenty patients with infectious spondylitis have been seen at the Mayo Clinic. Fifteen were males and 5 females. The average age was 34.1 years, the youngest being 9 and the oldest 59 years old. The average duration of the acute symptoms was twenty-one and six-tenths weeks, the shortest being six weeks and the longest two years. Twelve patients had a history of previous infection. In some the onset seemed to follow a mildly severe backache for from one to two weeks. A stage was then reached in which the patient was severely ill. All the

patients complained of pain. Fever was present at the time of onset in 16 cases. There were a spasm of the lumbar or psoas muscles or both in 18 cases, limitation of motion in 17 cases and tenderness over the affected region in 17 cases. Roentgenograms during the acute phase are usually normal, but when a series is carefully followed diminution in the thickness of one of the intervertebral disks appears. If the patient is followed over a period of months, increased thinning of the space and later proliferation of new bone along the margins of the involved vertebrae are observed. Finally solid bony fusion may be noted. In the earlier stages there may be some thickening of the paravertebral soft parts. This is not constant. If extensive vertebral involvement is present a diagnosis of osteomyelitis of the spine should be made, but when only the disk and the adjacent portion of the vertebral body are involved the condition is not true osteomyelitis. In cases of more advanced lesions, with obvious thinning of the disk in the roentgenogram, the differential diagnosis is narrowed to tuberculosis, post-traumatic thinning of the disks, typhoid spine, infection with Brucella abortus or Brucella melitensis and congenital absence of disks or fusion of vertebrae. A diagnosis of tuberculosis is justified when the onset is slow and insidious, with mild symptoms associated with tuberculosis of some other organ. In infectious spondylitis the onset is often more violent, or it is preceded by some acute infectious process elsewhere and leads to much more rapid and spontaneous healing, with fusion of the adjacent vertebrae as the usual end result. Osteomyelitis of the vertebrae in the more advanced stage presents a much more serious and prolonged disease than infectious spondylitis. Typhoid spine is almost, if not exactly, identical. Infection with B. abortus or melitensis, congenital absence of disks or fusion of vertebrae is usually readily recognized. The prognosis is excellent, both as to ultimate recovery with little or no disability and as to mortality. Only 1 of the authors' patients died. Two of the 20 patients have persistent symptoms. Two have not been observed recently. Patients with fever, prostration and extreme pain must be treated symptomatically, sedatives being used until the diagnosis is established, when a snugly fitted plaster of paris body cast on a Goldthwait frame is used to fix the spine during the acute phase of the disease. Pain will usually subside, and after two or three months sufficient healing will have taken place to permit the use of a steel brace or a corset. Such support must be continued until the symptoms have cleared up, perhaps for a year or more. In cases of persistent pain, fusion has been advised, but was done in only 1 case.

J. A. M. A.

CHILDBIRTH AFTER PRESACRAL NEURECTOMY. T. V. PEARCE, Brit. M. J. **1**:87 (Jan. 20) 1940.

Pearce reviews the opinions of various writers in recent literature concerning the effect on labor of resection of the presacral plexus. It is generally agreed that presacral neurectomy has no deleterious effect on the process of pregnancy or labor. Cotte reported that over 50 in a series of 300 patients undergoing presacral neurectomies had subsequent pregnancies and uncomplicated parturitions. Cases have been reported in which, after sympathetic neurectomy, the first stage of labor was painless and rapid or was not observed. Pearce reports the case of a woman with a history of dysmenorrhea and two long and painful labors on whom a presacral neurectomy was subsequently done. Two years after the operation she gave birth to a boy, with an easy and rapid labor. The author believes that the neurectomy was probably responsible for the absence of obstetric difficulties in the patient's third delivery.

ECHOLS, New Orleans.

PRIMARY LATERAL SCLEROSIS OF SOUTH INDIA: LATHYRISM WITHOUT LATHYRUS. R. L. H. MINCHIN, Brit. M. J. **1**:253 (Feb. 17) 1940.

Minchin analyzed 21 cases of spastic paraplegia of obscure origin occurring in natives of South India. After discarding all known causes for spastic paralysis, he concluded that the syndrome of paraplegia manifested in these patients was

identical with that of lathyrism. Despite the fact that Lathyrus sativus is probably never ingested by the inhabitants of South India, Minchin believes that the nervous syndrome exhibited by the patients in his series is identical with lathyrism; this suggests that lathyrism is a deficiency disease not necessarily connected with L. sativus or any other grain. Minchin believes that if a deficiency in diet is responsible for this condition, the absence of tryptophan in the diet of these natives is the probable causative factor in the development of the syndrome.

ECHOLS, New Orleans.

NERVOUS COMPLICATIONS OF WEIL'S DISEASE. VAGN MORTENSEN, Lancet **1**:117 (Jan. 20) 1940.

Mortensen reports a case of Weil's disease in a farmer aged 59, with recovery. The patient, previously in good health, became acutely ill with fever. There were conjunctivitis, muscular tenderness, headache, dizziness, bradyphrenia, nuchal rigidity and a positive Kernig sign. Jaundice was also present. Albumin and casts appeared in the urine; lymphocytes and albumin were increased in the spinal fluid. The cerebral meningeal symptoms became accentuated three weeks after the onset of the illness, and after initial apparent, but transitory, improvement there appeared complete flaccid paraplegia. The deep tendon reflexes of the lower extremities were absent. After six weeks the patient was discharged "feeling perfectly well and walking almost normally." Atypical serologic features were observed in this case, but the organism was found to be Leptospira sejr.

The extraordinary feature of this case was the presence of the flaccid paraplegia. This has been reported in only 4 cases before. In 2 of these 4 cases there occurred, in addition to the paraplegia, paralysis of the bladder, which was explained on the basis of transverse myelitis. In the first of the 4 cases, reported in 1935 by Creyx, Georget and Bonnel, a man aged 28 was infected with Leptospira icterohaemorrhagiae.

It has been thought that the morbid anatomic changes in the central nervous system in cases of Weil's disease are explained by ischemia of the meninges and parenchyma of the brain due to "terminal impairment of the circulation" (Bingel). Thus, cerebral symptoms are encountered often in patients with Weil's disease. True meningitis with cellular changes and spirochetes in the spinal fluid may occur in 10 per cent of cases (Schüffner and Walch-Sorgdrager, 1936). Peripheral neuritis may also be a manifestation of this disorder. Weil's disease may be present without jaundice, and obscure meningitis may be the only indication of this spirochetal infection.

KRINSKY, New London, Conn.

SCIATICA AND THE INTERVERTEBRAL DISK. J. PENNYBACKER, Lancet **1**:771 (April 27) 1940.

Pennybacker's report is concerned with 30 consecutive cases of sciatica in which treatment has been given in the Nuffield department of surgery, Oxford, England, since May 1939. Since all the patients were operated on within the past nine months, it is too early to speak of ultimate results. The most dramatic relief was obtained in 21 cases of severe sciatica in which a loose fragment of prolapsed nucleus pulposus was removed. Most of the patients began to walk seventeen or eighteen days after operation, and although there were some soreness and stiffness of the back at first, these symptoms improved rapidly with graduated exercise, and by the end of a month the patients were free from symptoms. Of the 5 patients who had herniation of the annulus fibrosus, 2 experienced immediate relief and had a painless convalescence. In 3 others the results of operation were not satisfactory. The 2 patients with the cauda equina syndrome were completely free of pain after operation, but recovery of sphincter control and of the sensory and motor functions has been slow. In 1 of the remaining cases the results of exploration were negative, but there have been considerable benefit from the laminectomy; in the other a fibroangioma was removed from the intervertebral canal, but this has

not completely relieved the pain. In no case has there been any aggravation of the symptoms or neurologic signs after operation. It appears that operation is advisable in three groups of cases: (1) those of acute sciatica which sends the patient to bed and which persists, despite adequate rest for from five to six weeks; (2) those in which there are frequently recurring attacks which may be severe enough to send the patient to bed or to make his life a misery for three or four weeks every year; (3) some cases of chronic continuous sciatica due to a prolapsed nucleus pulposus, in which the results of operation are no less satisfactory than in cases of the acute and severe form. In other cases in the group of chronic sciatica the pain is due to a herniated annulus fibrosus, and the results in these have not been as uniformly satisfactory as in those in which the cause is prolapse of the nucleus pulposus. Until it is possible to differentiate these varieties by the history and examination or by myelography, some doubt must remain about the value of operation.

J. A. M. A.

Vegetative and Endocrine Systems

RELATION BETWEEN THE GROWTH PROMOTING EFFECTS OF THE PITUITARY AND THE THYROID HORMONE. H. M. EVANS, M. E. SIMPSON and R. I. PENCHARZ, Endocrinology **25**:175 (Aug.) 1939.

A large group of female rats 35 to 45 days of age were parathyrothyroidectomized, and after an average period of three months evidence of the completeness of the operation was sought in the degree of depression of the basal metabolic rate and retardation in growth. Approximately 50 animals gave satisfactory evidence. In some cases all the structures in the thyroid region (trachea, esophagus, surrounding muscle) were removed and examined in serial sections for fragments of the thyroid. No such fragments were found in animals in which less than 130 liters of oxygen per square meter for twenty-four hours was consumed (normal 150 liters). The basal metabolic rates of the animals chosen for experimental purposes averaged 30 per cent below normal. Complete growth stasis occurred in the group. Some increase in weight occurred during the first ten postoperative days (12 Gm., as compared with a normal of 30 Gm.), then ceased until late after the thyroidectomy, when there was again some increase, due to adiposity, and not to skeletal growth.

The animals were divided into four groups of 5 or 6 each, as follows: (*a*) control animals not given injections; (*b*) animals given daily injections of 0.005 mg. of crystalline thyroxin, this dose having been found adequate for restoration of the basal metabolic rate to normal; (*c*) animals given daily injections of 1 cc. of a standardized alkaline extract of bovine anterior pituitary; (*d*) animals given injections of the last-mentioned extract with the addition of thyroxin, the thyroid and pituitary substances being injected at the levels employed in groups *b* and *c*. Similar numbers of normal control female rats, as nearly as possible of the same body weight as the thyroidectomized animals, were given injections of thyroxin, anterior pituitary and the combination of these two substances. The results show that after three months the largest giants produced in the experiments were rats given injections of the combination of anterior pituitary and thyroxin and that no differences existed between thyroidectomized rats so treated and normal rats. Normal animals given injections of the pituitary extract alone were very large, but were significantly smaller than the animals treated with both anterior pituitary and thyroxin. Thyroidectomized animals treated with anterior pituitary were next in size and were appreciably larger than any normal control rats. Thyroidectomized animals treated with thyroxin alone had conferred on them a normal growth rate, the untreated thyroidectomized controls remaining dwarfed. The treatment of normal animals with thyroxin did not modify their growth. These experiments seem to show that growth promotion in excess of normal secured by anterior pituitary extracts is not conditional on the presence of the thyroid, but is greater when the thyroid is present and that in thyroidectomized animals it is equally great if thyroxin is concomitantly administered.

Characteristic ovarian changes are found after thyroidectomy of long standing. These consist essentially in the substitution of medullary for cortical activity, growth of the so-called medullary or hilus tubules occurring. In extreme cases the latter structures dominate the ovary, ovarian follicles and corpora lutea. Normal interstitial tissue is absent.

PALMER, Philadelphia.

PHYSIOLOGICAL CHANGES IN THE ANTERIOR HYPOPHYSIS OF VITAMIN A–DEFICIENT RATS. T. S. SUTTON and B. J. BRIEF, Endocrinology **25**:302 (Aug.) 1939.

Sutton and Brief describe a technic for the assay of gonadotropic hormones in which the degree of gonad stimulation is measured by the changes in vaginal epithelium. It has been shown that this method of assay is three to five times as sensitive as the ovarian weight method. The sensitivity of this technic is illustrated by the fact that 0.14 mg. of anterior lobe of the pituitary gives a measurable stimulation. With this technic, the anterior lobes of the pituitary gland from normal and from vitamin A–deficient rats were assayed for gonadotropic activity. The data obtained show that pituitary substance from normal males has greater gonadotropic activity than that from normal females. In vitamin A deficiency the gonadotropic hormone content of the pituitary gland is increased. This increase in potency is greater in the male than in the female. This study provides further evidence that vitamin A deficiency exerts direct damage on the gonads. The increase in elaboration of gonadotropic hormones represents a compensatory change in the hypophysis similar to that which occurs after castration.

PALMER, Philadelphia.

THE EFFECT OF ESTROGEN ON THE SKELETAL AGE OF IMMATURE RATS. N. B. TALBOT, Endocrinology **25**:325 (Aug.) 1939.

Beginning on the first day of life, a number of rats were given daily injections of 12.5 micrograms of estradiol benzoate. A satisfactory number of rats served as normal controls. All the animals were suckled by the mothers until the eighth or tenth day of life, when they were killed with chloroform and the progress of ossification was studied. The data obtained show that estrogen causes a distinct increase in the size and number of ossification centers in the females, but not in the males of the same age. The treated females had an average of 32 per cent more centers than the control females, whereas the mean difference between the treated and the control males was 2 per cent. The authors suggest as a possible explanation that male mice do not respond to estrogen as rapidly as female mice, since testosterone may inhibit the action of estrogen on bones.

PALMER, Philadelphia.

RESPONSE OF CHRONICALLY FATIGUED NEUROTIC PATIENTS TO ADRENAL CORTEX THERAPY. J. H. HUDDLESON and R. A. MCFARLAND, Endocrinology **25**:853 (Dec.) 1939.

Huddleson and McFarland gave orally glycerinated adrenal cortex (pills) to 14 patients suffering from psychoneuroses marked by asthenia. The experimental period for each patient was from ten to fifteen weeks. There was one week of no medication, followed by two weeks of placebos. These three weeks, and occasionally a week later on during which placebos were given, served as controls. The increasing doses of adrenal cortex ranged from 15 to 48 pills daily, each pill representing 3 grains (0.2 Gm.) of fresh gland. Half the patients reported subjective improvement. Half gained a kilogram (2⅕ pounds) in weight. The basal metabolism rate was accelerated (improved) in 8 patients. Nine patients showed improvement, and 5 no change, in the Schneider index. The inventories of psychologic and of physiologic complaints showed improvement, respectively in 7 and 6 of the 10 patients tested. The word association test indicated fewer neurotic responses in 7 patients, neuromuscular coordination was improved in 5, and per-

severation was lessened in 4. After the medication, objective tests showed improvement in more than half the patients. Seemingly, this treatment has proved valuable in treatment of obstinate asthenic psychoneurosis. J. A. M. A.

ACROMEGALY AND DIABETES MELLITUS. C. COGGESHALL and H. F. ROOT, Endocrinology **26**:1 (Jan.) 1940.

Coggeshall and Root discuss the occurrence of diabetes in 26 of 153 patients with acromegaly, evidences of hyperpituitarism with excessive height in 3 patients with diabetes and frank acromegaly and gigantism each in 3 patients. In the 26 patients with diabetes and the 3 patients with hyperpituitarism, the average intervals between the onset of acromegaly and that of diabetes was nine and two-tenths years. A constitutional or hereditary predisposition to diabetes encountered in association with acromegaly is suggested by the existence of hereditary or familial diabetes in 6 of the 29 patients, or 21 per cent, whereas of the relatives of the 127 patients having acromegaly without known diabetes only 2 per cent had diabetes. The obesity of 113 patients with acromegaly resembled that of diabetic patients in that 73 per cent of the acromegalic patients had been from 10 to 70 per cent above standard weight. Absence of the specific dynamic action of protein was observed in 1 case of acute hyperpituitarism at the beginning of a period of treatment for diabetes; a subsequent test after treatment showed normal specific dynamic action. During this period the basal metabolism fell from + 34 to + 1 per cent. Comparison was made of the weights of organs at necropsy in groups of patients with acromegaly, diabetes, combined acromegaly and diabetes and Simmond's disease. Splanchnomegaly occurred only in the presence of acromegaly. Its absence in cases of ordinary diabetes argues against the possibility that persistent hyperpituitarism caused the diabetes. The possibility remains that a brief period of acute hyperpituitarism could produce permanent damage to the islands of Langerhans without splanchnomegaly. However, diabetes did not develop in 4 cases of fugitive acromegaly due to mixed tumors of the pituitary. At necropsy in 50 cases of diabetes, variations in the size of the pancreas were not associated with variations in the weight of other internal organs, such as was shown in cases of acromegaly and Simmonds' disease. The clinical character of the diabetes associated with acromegaly does not show any greater variation in severity, resistance to insulin and duration of life than is seen in a large group of diabetic patients without acromegaly. An inconsistency between a blood sugar curve indicating insensitivity to insulin and the fact that the patient had repeated insulin reactions was observed. The usual complications of diabetes, including pyogenic infections, arteriosclerosis with gangrene and coronary atherosclerosis, occurred. Coma may develop in cases of acromegaly with diabetes, and therefore the same careful adjustment of diet and insulin is required as in cases of diabetes of similar severity without acromegaly. In certain cases of mild acromegaly and diabetes excessive polyphagia without loss of weight or development of acidosis resembled the diabetes produced by Young by the injection of anterior pituitary extract. His demonstration that degeneration of the islands of Langerhans and chronic diabetes can be produced in the dog by injection of large amounts of crude anterior pituitary extract of the cow provides a new method of studying the possible production of similar changes in the human subject with diabetes by such a diabetogenic substance. J. A. M. A.

Treatment, Neurosurgery

THERAPEUTIC QUARTAN MALARIA IN THE THERAPY OF NEUROSYPHILIS AMONG NEGROES. T. C. C. FONG, Am. J. Syph., Gonor. & Ven. Dis. **24**:133 (March) 1940.

An analysis of the results of therapeusis with malaria of the quartan type showed that 229, or 53.2 per cent, of a group of 436 Negro patients with neuro-

syphilis responded successfully to inoculation. This was a far greater response than that following inoculation with tertian malaria, but it is considerably lower than the figures given by other authors. Of this number, 13.9 per cent were found to be much improved by treatment, 33.1 per cent were improved and 52.8 per cent were not improved. Thirty-eight, or 12.2 per cent, of the successfully inoculated group died of causes not directly attributable to malaria. The deaths of 6, or 2.5 per cent of the entire group inoculated, were due directly to therapeutic use of quartan malaria. There appeared to be no definite correlation between clinical and serologic improvement or vice versa, except that the majority of patients who were clinically improved revealed concomitant serologic improvement. Finally, quartan malaria may be regarded as more effective than tertian malaria in the therapy of neurosyphilis among Negroes.

BECK, Buffalo.

QUARTAN MALARIA IN THE TREATMENT OF NEUROSYPHILIS. MARK M. KROLL, Am. J. Syph., Gonor. & Ven. Dis. **24**:148 (March) 1940.

Kroll reports on 62 patients, 46 Negroes and 16 white persons, who had been inoculated with the organism of quartan malaria in treatment of neurosyphilis. The use of quartan malaria was suggested because of its low incidence, for which there has been no satisfactory explanation. Certain patients, though in need of malarial therapy, prove to be resistant to the tertian varieties. The resistance acquired is highly species specific, and is at times mutually exclusive even to different strains of the same species.

All patients were given intravenous injections of citrated blood; the strain used was obtained from a patient with natural infection. In 7 patients, or 11.3 per cent, quartan malaria failed to develop. The average period of incubation was thirteen and four-tenths days for white persons and nineteen and three-tenths days for Negroes, but in 2 patients the chills appeared only after seventy-five and ninety-seven days, respectively. The patients were allowed to have from ten to fifteen paroxysms unless there was spontaneous regression or some complication. The chills in general were less severe and of shorter duration than those occurring with tertian fever. The average height of the paroxysms ranged from 104.5 to 106 F. Relatively few complications were encountered, and these were easily handled. Moderate degrees of anemia resulted frequently, and in 1 patient there developed methemoglobinemia. Renal complications were more common in patients who had had previous impairment of the kidneys. In 2 patients jaundice developed; 2 patients became confused, and 1 had a convulsion. One patient died of pneumonia five weeks after the onset of malaria. Quinine sulfate was used to terminate the fever. When relapses occurred, atabrin or plasmochin, or both, were used in combination with quinine. When both a tertian and a quartan strain were injected simultaneously, the tertian was usually found to be dominant. No precautions were taken with the patients to prevent spread of the infection.

Of the cases reported by Kroll, no progression was shown in 11 cases of asymptomatic neurosyphilis. Twenty-three patients with dementia paralytica were followed; 5 regained former levels, 10 showed incomplete remission, 5 showed little or no improvement and 3 died. Of 13 tabetic patients, 12 showed varying grades of relief. Of 5 patients with meningovascular syphilis, improvement was noted in all. Neither the serologic reactions of the blood nor the complement fixation reaction of the spinal fluid was significantly altered. No direct correlation was found between clinical and serologic improvement.

BECK, Buffalo.

THE UNTOWARD REACTIONS OF TRYPARSAMIDE. I. KOPP and H. C. SOLOMON, Am. J. Syph., Gonor. & Ven. Dis. **24**:265 (May) 1940.

Kopp and Solomon report their experience with the untoward or toxic manifestations of tryparsamide during the six years between 1923 and 1929, during which 43,308 injections were given to 829 patients. Most observers agree that visual disturbances are most apt to occur during the first 12 injections of the

drug and that if the patient is repeatedly questioned concerning disturbances in vision early detection is possible and immediate discontinuance of the drug will prevent serious damage. Subjective complaints consist of blurring of vision and "spots before the eyes." Optic atrophy occurred in 10 patients. It is suggested that the type of syphilitic lesion may play an important role in the development of optic atrophy. It was present in 43 per cent of patients with tabes dorsalis, in contrast to 24 per cent of patients with dementia paralytica. When visual disturbances begin after the patient has had 17 injections or more, optic atrophy is unlikely to result. Treatment for toxic amblyopia consists of immediate withdrawal of the drug and, if there is objective damage, forced drainage of spinal fluid.

Nitritoid or allergic reactions are rarely observed, but usually appear in patients who have shown other manifestations of reaction. They are more frequent in patients who have received a considerable amount of tryparsamide. The reaction is frequently ushered in by paroxysmal coughing, and may be followed by sweating, flushing, coryza, substernal discomfort, nausea, vomiting, diarrhea, collapse and convulsions. These reactions may be mild or very severe.

The gastrointestinal reaction is most common. It occurs more frequently after prolonged use of the drug. The reaction may develop immediately or as late as four hours after administration of the drug. Nausea, vomiting, diarrhea and abdominal cramps occur, and may be accompanied by perspiration, apprehension, dizziness, chills and fever. Recurrences can be avoided in most patients by reducing the dose of the drug.

Jaundice due to tryparsamide is usually benign and brief, with few symptoms and no sequelae. In some patients other signs of sensitivity to tryparsamide occur prior to the appearance of the jaundice. The stools are clay colored at first and the urine contains bile. The liver may be enlarged, but is not tender. Treatment consists of a diet high in carbohydrates and low in fats and administration of magnesium sulfate by mouth and duodenal tube.

Cutaneous lesions occur usually in patients who have exhibited other signs of sensitivity to tryparsamide. These lesions may consist of desquamated patches on an erythematous base, red blotchy papules and small purpura-like areas which involve the wrists, fingers, arms, legs, shoulders and forehead. The lesions may be large or small, and are accompanied by pruritus.

Cerebral reactions, such as dizziness, may occur after administration of tryparsamide. Dizziness, headache, drowsiness, nausea, vomiting and weakness, coma, severe headache and convulsions, as well as an acute auditory or visual hallucinosis with excitement, have been noted. Patients with tabes dorsalis have experienced exacerbation of lancinating pains. Tremors of the facial muscles and fingers may be exaggerated early in the course of tryparsamide therapy. In some patients it is possible to continue treatment by reducing the dose of the drug, but in others these reactions continue and the drug must be omitted.

BECK, Buffalo.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

H. Douglas Singer, M.D., *President in the Chair*

Regular Meeting, April 4, 1940

Mental Depression as an Equivalent of Migraine. Dr. Donald A. R. Morrison, Oconomowoc, Wis.

Many theories have been proposed to explain the cause of migraine, but none of them has been found completely satisfactory. In general, migraine is best understood as a discharge of nervous energy through sensory and autonomic pathways. In recent years there has been a growing interest in the psychologic factors in migraine, and various authors have noted the significance of emotional elements in the causation of this disorder. Some writers have emphasized the importance of unconscious aggressive impulses. Five cases were observed in which the migraine ceased when a state of psychotic depression developed. In 2 cases in which the patient could be followed it was found that the migraine returned when the depression subsided. Since in a depression the aggressive impulses are directed against the patient himself, it is concluded that in the cases presented the attacks of migraine allowed somatic expression of tension motivated by undischarged aggressive impulses.

DISCUSSION

Dr. David Slight, Chicago: One might well return to Liveing and Gowers for a simple and clear statement of the essential nature of migraine. The semi-popular description by Liveing of the disorder as a "nerve storm" does at least remind one that the disorder is one of the nervous system, which seems to be forgotten in many modern theories.

For some years at the University of Chicago my associates and I have been interested in studying the interrelationships of migraine and other forms of neuroses. Thus, we find in a larger proportion of migrainous subjects than is noted in the textbooks either replacement of the migrainous attack by other episodic disturbances or the development of neuroses, such as neurodermatitis, anxiety and obsessional states, with disappearance of the migrainous attacks.

Dr. Morrison has described a few cases in which such a depressive reaction supervened. We could add to the series; indeed, I saw 1 such case today. In addition to such severe and lasting depressions, one should also keep in mind the many cases in which the depression is of lesser degree and lasts for only a few days, but approximates, nevertheless, the psychotic depressions.

Dr. H. Douglas Singer, Chicago: Is it not probable that the situation with regard to migraine is similar to that with regard to epilepsy? Is there one type of migraine? Or is there a whole group of migraines with various etiologic factors? In view of the extreme frequency of migraine, why is it that one picks up only a few cases in which there are also definite attacks of psychosis? If the two conditions are so closely related, why are there not more such cases? Can Dr. Morrison give the percentages of persons with migraine with and without psychosis? If the cause is some psychic conflict, what is the basis for the unilaterality of migraine? Many attacks of migraine come on during sleep, and not as the result of some particular complication at one time. Dr. Slight mentioned a group of cases, not extremely rare, in which migraine was associated with ophthalmoplegia, and another in which there was neural palsy. How shall these be explained?

DR. DONALD A. R. MORRISON, Oconomowoc, Wis.: In regard to Dr. Singer's question as to whether migraine may be compared with epilepsy in that a number of conditions are put into one group, it has been my experience that migraine cannot be classified in this fashion, but must be considered as an entity, and that the most important causative factor is the psychologic one. Dr. Singer has also raised the question why there are so few cases in which psychoses are related to migraine. Migraine is often overlooked because it is not inquired about, and in general history taking little mention is made of it. I am unable to explain the unilaterality of the headaches. It seems to me, however, that it is just as easy or as difficult to explain on an emotional basis a generalized headache as a unilateral one. With regard to the onset of an attack of migraine during sleep, I think that does not contradict the theory of an emotional basis for migraine, for a patient may dream or be disturbed during sleep as well as when awake. The headache may come from internal as well as from external stimuli. Ophthalmoplegic migraine is generally regarded as different from idiopathic migraine, and when there is definite neural paralysis one looks for organic lesions.

Dr. Slight has pointed out that the equivalents are not always as clearcut as those I reported. Many are rather indefinite, and unless one anticipates that migraine may have been present, the relationship is apt to be overlooked.

Impotence: Its Treatment by Certain Endocrine Products. A Preliminary Report. DR. HUGH T. CARMICHAEL, DR. ALLAN T. KENYON and DR. WILLIAM J. NOONAN, Chicago.

Disturbances in any one of the four functions on which normal intercourse depends, namely, sexual desire, erection, ejaculation and orgasm, may be caused by organic or nonorganic factors or a combination of the two. The majority of patients who suffer from impotence fall into the group in which thorough physical examination and laboratory studies, including all indicated special tests, reveal insufficient or no evidence of: first, definite structural changes in the genitourinary apparatus; second, obvious endocrine dysfunction, and, third, demonstrable neurologic disorder. In man and in many animals it has been proved conclusively that the attainment of complete sexual development and the ability to carry out the normal sexual functions of intercourse and procreation are directly dependent on the possession of adequately functioning testes, although in man the capacity to have erections, to sustain them sufficiently for intercourse and to experience at least a form of orgasm is not always strictly dependent on the testis. After castration these functions may remain intact for long periods or diminish to varying degrees. The anterior lobe of the pituitary gland is also closely related to efficient gonadal function, as has been shown repeatedly in experimental animals and in the gonadotropic effects of preparations of the anterior lobe of the pituitary used clinically in man. Androgen, in the form of testosterone propionate, has been shown to induce definite biochemical changes in eunuchoid persons and in normal men and women. It has been found to be most effective therapeutically in cases of hypogonadism, such as eunuchoidism. Its tentative use in the treatment of the type of impotence previously described seems warranted, since it cannot be denied with certainty that there may be a deficiency of the internal secretion of the testis in some cases of impotence, and since it has not been proved beyond a doubt that testosterone propionate may not exert some stimulating action on the sexual drive in man.

We have used testosterone propionate, in 25 mg. doses, three times a week, in a group of men who complained of varying forms and degrees of impotence and who did not show obvious endocrine dysfunction, neurogenic disease or marked structural changes in the genitourinary tract. We tried to avoid psychotherapeutic effects by making no attempts at psychotherapy during the course of the experiment. Satisfactory relief of the impotence was obtained by about one third of the patients. In these patients potency was maintained when sesame oil was substituted for the testosterone propionate without the patient's knowledge and also when all injections were stopped. This suggests that the good results cannot

be attributed to the effects of the testosterone propionate alone and makes it reasonable to assume that, in part at least, the effects were psychologic. But how may one explain these successful results and the failure of response in the rest of the patients? Would it be permissible to conclude that improvement or failure is directly correlated with the depth and degree of the neurotic conflicts which may be present? It is questionable whether any degree of deficiency in testicular secretion would not have been compensated for by the dose of androgen used. While it is desirable to secure experience with larger amounts of the agent, our present impression is that neurotic conflicts play an important part in determining the nature of the results. In those in whom great anxiety was not produced by the testosterone propionate beneficial effects were observed. In the other patients so much anxiety and fear were induced that the inhibition of sexual functions persisted unchanged.

DISCUSSION

DR. THERESE BENEDEK, Chicago: Not only is this paper interesting but it seems to be the preliminary report of an important investigation. The work is partly done in these 18 cases, and has partly yet to be done, either in the same cases or on new material, for it seems that a thorough study of the endocrinologic factors and of the psychodynamic structure in cases of psychic impotency would give pertinent information about this syndrome.

In this paper, which is admittedly not yet based on such thorough psychoanalytic studies, the main classificatory aspect is that 7 patients were cured permanently by testosterone propionate, 1 was cured for a short time and 11 were not cured. Thus, the conclusion, or rather the assumption, is that the effect of the testosterone is "psychologic," not physiologic. I feel that I am in the peculiar position of protecting the physiology against the physiologist; but one should not quarrel over words. After all, psychology is also only one aspect of physiology. I should rather take issue with the wording of the authors. The 7 patients who were cured wanted to be cured; the others did not. This sounds much like some expressions of old times, when the patient's will power, the capability of regaining freedom from symptoms or the lack of it, was called "psychologic." But I know that the authors meant it differently. They meant that in the 7 cured patients the psychologic conflict inhibiting the sexual potency was such that a reaction to testosterone could relieve the anxiety and cure the symptoms. I do not see any evidence that the authors believe that these 7 patients would have reacted in the same way to injection of sesame oil alone. If that were the case, then of course testosterone would have only a suggestive effect. On the basis of few observations, I had the impression that one is not justified in assuming that the effect of testosterone is only suggestive. In 1 of the cases to which the authors refer, the specific emotional effect of testosterone could be observed. Thus, I believe the problem which the authors encounter in their further investigations is this: Which patients are easily influenced by testosterone and which are not? Some of the answers are given even in this short summary. One is the assumption that the difference may lie in the lack of the man's own hormone production. One eunuchoid patient I know was surely lacking in self-produced hormone and reacted positively to the substitute therapy with testosterone, but only after he had also had treatment with a preparation containing gonadotropic substance from the urine of pregnant women.

In cases in which there is not such obvious endocrine disturbance as that in eunuchoidism, the negative therapeutic reaction to testosterone might have the following basis: Anxiety interferes with sexual potency. The reason for the anxiety is repressed, and often the anxiety is not conscious. The impotency covers the anxiety. It is not necessary to be afraid; the danger is avoided by the symptom. The reaction to testosterone would be the increase of the inner psychic conflict, and the patient would respond either with overt anxiety or with other symptoms which help to avoid the anxiety. But surely one of the most important of them is the impotency; thus, these patients will not react positively to treatment

with testosterone alone. But this fact can be explained also as a psychologic reaction on the basis of this psychodynamic response. The patients who are easy to treat, who can overcome the anxiety by increased physiologic substratum, react positively to progesterone. The difficult ones, also those with great repressed anxiety, even when they want to be helped, cannot use the physiologic help. They must be made free by psychotherapy—psychoanalysis—to be able to react to the physiologic agent.

This important work done in the University of Chicago will help to differentiate the patients who can be helped without psychcanalysis. Only thorough psychoanalytic study could help to clarify the problems of the combined therapy: therapy with hormones and with psychotherapy.

Dr. Allan T. Kenyon, Chicago: My interest in this work arose because of the great sexual stimulation one observes in the eunuchoid cn treatment with testosterone. I felt that one often was not clear as to whether there was or was not a normal amount of testicular secretion in men with well established secondary sex characters. Even after castration there may be little recession cf the signs of testicular activity, and alterations in size of the prostate are not useful if the initial size is not known. Thus, I felt it was possible that we were overlooking instances of testicular insufficiency expressing itself as impotence. Accordingly, I was sanguine about treating such patients with androgens. However, no dependence on testosterone was established, as there would have been, I believe, if testicular deficiency had been genuine. I believe with Dr. Benedek that there may be such instances, but more extended study will be necessary to reveal them.

Dr. Hugh T. Carmichael, Chicago: I am grateful to Dr. Benedek and Dr. Kenyon. They have covered a number of questions which might have occurred to any one. I feel that Dr. Benedek has touched on an important aspect—that impotence may cover repressed anxiety, and that when testosterone propionate is given there may be reactivation of the anxiety. If the anxiety and fear are extreme the impotence may be much more pronounced. If the conflicts are not too severe the anxiety will be less, and sufficient impetus may be provided to induce return to potency.

Basal metabolic rates were estimated only for those patients in whom we thought there was some indication for the procedure. We have not had experience with thyroid medication in these patients; perhaps it would be effective.

Further Analysis of Grouping Behavior in Patients with Cerebral Injury.
Dr. Ward C. Halstead, Chicago.

In analyzing the grouping behavior of (1) patients with lesions of the frontal lobe, (2) patients with cerebral lesions posterior to the frontal lobe and (3) normal persons, use has been made of Klüver's method of "equivalent and nonequivalent stimuli." Examination of the groups made by the various subjects in terms of this method revealed the existence of four general types. Patients with lesions of the frontal lobe produced a smaller total number of groups on the average. Such patients were also differentiated in terms of the relative frequency with which groups of certain types were produced.

DISCUSSION

Dr. Henry W. Brosin, Chicago: The work reported tonight and the series of experiments on which Dr. Halstead has been engaged for the past five years are of especial interest to the psychiatrist, as they point to a specific attack by a fruitful method on a major problem in his field. It is often said that psychology should be to psychiatry what physiology is to internal medicine, but the clinician in the past has found little beyond intelligence tests to help him in his effort to study personality or thinking. Since "quantitative" tests have yielded so little, one looks to the "qualitative" methods for help. The investigations of Rawlings, Wentworth, Babcock, Bender, Bolles, Goldstein, Hanfmann and Kasanin, Rickers

and Cameron have broken the ground for study of thinking disorders, and have led one to expect that by this means one could describe a psychotic person sufficiently well to be of primary use in evaluating the personality and the prognosis, and eventually of aid in treatment. The selection of patients with the best prognosis for "shock therapy" is such an immediate clinical application of an apparently remote subject.

Dr. Halstead has chosen to study thinking at the level of abstraction. He does not assume that abstract behavior is a crowning achievement of the physiolcgic hierarchy and hence unavailable to objective analysis, as is customary in some texts. Instead, using the method of thoroughly exploring the potentialities of the individual patient in categoric and other experiments, he demonstrates again that thinking and thinking disorders can be studied experimentally in the best tradition of the scientific method. The unusual care necessary to prepare and maintain a patient in order to obtain genuine participation in experiments of this character is an important lesson to those who hope that these experiments will be of general clinical significance.

The question is raised whether abstractness is a field property. Goldstein's well known work has a resolution in terms of concreteness and abstractness, but Dr. Halstead's paper raises the further question of how these properties can be defined more precisely in experimental settings. In what terms can relative concreteness or abstractness be best demonstrated? The conclusion that the individual patient's ability to manipulate many series of related operations must be understood before it is possible to grade the relative concreteness of his behavior will be acceptable to those who subscribe to the belief that the person must be understood as a whole before predictions can be made. One sees here an effort to avoid the fallacy of measuring so-called unitary functions in isolation, by using devices which compel attention to be directed to the total field in which the behavior in question occurs. The important, but neglected, fact that an experimental field may "require" abstractness in a particular manner is emphasized, as well as the fact that some persons may utilize as concrete something which one ordinarily thinks of as abstract. This is seen in the fields of mathematics and music, yet it escapes ordinary quantitative methods of examination.

Beginning in the basic field of the organic, one can see constructive methods being developed which should be of use in other fields in which thinking disorders are apparent. That the technic is difficult of application and the theory supporting it complex need not be intimidating, for beginnings are often puzzling. Hopeful is the fact that there is an objective means of tackling a problem which has heretofore eluded laboratory analysis.

I should like to have Dr. Halstead discuss the advantage of the qualitative over the quantitative method in investigating abstract behavior.

Dr. Benjamin Boshes, Chicago: I have heard Dr. Halstead present this material before, and in general I concur with his thesis. There is one point that is worth mentioning. In cases of defects in the brain the functional alteration which occurs is not necessarily related to anatomic location. This is particularly true when one is dealing with a lesion such as a tumor. It has been pointed out that the most extensive disturbance in mental function occurs in cases of temporal and parietal tumors. It would appear that intracranial hypertension is an important factor in such cases. I remember a patient with a tumor of the occipital lobe whose only "localizing" symptom was Witzelsucht. He was demented and completely blind when I first saw him, the blindness being due to severe optic atrophy subsequent to choked disks. I am certain that with the tests discussed tonight the pathologic lesion would have been referred to the frontal lobe, although anatomically it was in the occipital lobe. I should say, therefore, that one must consider not only the anatomic but the physiologic localization. To exclude the latter would mean correlating the psychologic defect with elements that may play only a partial role in the total picture.

Dr. Ward C. Halstead, Chicago: Time does not permit an adequate consideration of the question raised by Dr. Brosin. In this report I have focused

attention on the findings obtained in patients with lesions of the frontal lobe. It remains to be seen, of course, whether future work will support the observation that the grouping behavior of patients with lesions of the frontal lobe is characteristically different from that of patients with other cerebral defects and of normal persons.

Dr. Boshes seems to have misunderstood the type of material on which my findings are based. In every instance, the patients with cerebral injury were neurosurgical patients.

The many investigations in this field point clearly to the fact that future progress in the analysis of cerebral function is dependent on analysis of basic mechanisms in behavior. In this connection, one can only repeat that it seems more important at present to study the existence or nonexistence of certain types of grouping behavior in cases of cerebral lesions in general than to make statements about the symptomatology of involvement of different lobes of the brain.

CHICAGO NEUROLOGICAL SOCIETY

RICHARD B. RICHTER, M.D., *President in the Chair*

Regular Meeting, April 18, 1940

Anatomic Changes Secondary to Temporal Lobectomy. DR. PAUL C. BUCY and DR. H. KLÜVER.

In recent publications (Klüver, H., and Bucy, P. C.: "Psychic Blindness" and Other Symptoms Following Bilateral Temporal Lobectomy in Rhesus Monkeys, *Am. J. Physiol.* **119**:352-353, 1937; An Analysis of Certain Effects of Bilateral Temporal Lobectomy in the Rhesus Monkey, with Special Reference to "Psychic Blindness," *J. Psychol.* **5**:33-54, 1938; Preliminary Analysis of Functions of the Temporal Lobes in Monkeys, ARCH. NEUROL. & PSYCHIAT. **42**:979-1000 [Dec.] 1939), we have discussed the striking alterations in behavior that consistently develop in rhesus monkeys after the removal of both temporal lobes. The following symptoms can be observed:

1. *"Psychic Blindness."*—Although the animal retains essentially normal vision, it seems unable to recognize the nature of objects on the basis of visual perception alone. Some observations suggest that in addition to visual agnosia there may be auditory, and possibly tactile, agnosia.

2. *Oral Tendencies.*—There exists a strong tendency to examine every object by mouth and to smell it. The oral examination consists of licking, biting gently, chewing and touching with the tongue and lips.

3. *"Hypermetamorphosis"* (in the sense of Wernicke).—There is a strong tendency, which appears to amount to a compulsion, to attend and react to every visual stimulus.

4. *Emotional Changes.*—We find absence or marked diminution of those motor and vocal reactions generally associated with anger and fear in the rhesus monkey. The animal tends to approach all animate and inanimate objects without hesitation.

5. *Changes in Sexual Behavior.*—Whereas the previously mentioned symptoms appear immediately after the operation, the changes in sexual behavior occur only after the lapse of several weeks or months. There is a striking increase in the amount and diversity of autosexual, homosexual and heterosexual behavior.

6. *Change in Dietary Habits.*—One of the most striking changes is that the monkeys accept animal foods immediately after bilateral temporal lobectomy and eat large quantities of ham, bacon, ground beef, liver sausage and other meats. Such rhesus monkeys as we have observed under laboratory conditions are frugivorous and usually will not even touch meat when it is offered to them.

In order to determine what structures must be destroyed in the brain to provoke these changes in behavior, we have endeavored to learn from the available material not only what structures were removed at the operations but also what tracts and nuclear structures have subsequently undergone degeneration.

This evening we present our observations on the brain in our first case, that of a mature female monkey *(Macaca mulatta)* from which the uterus and both ovaries had been previously removed. On Dec. 7, 1936, the left temporal lobe was removed. After this operation there was a marked change in the direction of greater "tameness." On Jan. 25, 1937, the right temporal lobe was removed. This operation was followed immediately by marked alterations in behavior which we have previously characterized as "psychic blindness," oral tendencies, "hypermetamorphosis" and profound changes in emotional behavior. These symptoms persisted essentially unchanged until the animal was killed two years after the first operation, on Dec. 7, 1938. It is of interest that even in this castrated female typical "presenting reactions" were frequently observed after a period of one and a half years.

General necropsy, including both gross and microscopic examination, revealed only the absence of the internal genitalia. The hypophysis, lungs, heart, lymph glands, liver, kidneys, adrenal glands, spleen, pancreas, stomach, intestines and urinary bladder were entirely normal.

The entire brain was fixed in dilute solution of formaldehyde U. S. P. (1 : 10), embedded in pyroxylin and cut in serial coronal sections, 25 microns thick. Every tenth section (section 10, 20, 30 and so on) was stained with cresyl violet and every twentieth section (section 5, 25, 45 and so on) according to Weil's method as modified by Keller. Additional sections were stained whenever they were required. Degeneration of myelinated fiber tracts was readily determined and studied by either or both of two changes, demyelination as present in the sections stained according to Weil's method and secondary gliosis as seen in the preparations stained with cresyl violet.

The following anatomic changes were observed:

1. Both temporal lobes were removed. The line of extirpation extended posteriorly along the lower border of the sylvian fissure to a point just posterior to the lower end of the rolandic fissure. Here it turned ventrally to cut across the first and second temporal convolutions. The rhinencephalon was extensively removed, only a fragment of the right amygdala and the most posterior part of the hippocampal formation, where it turns dorsally in the trigon of the lateral ventricle, remaining.

2 and 3. The temporofrontal fibers, which form the uncinate fasciculus and a temporo-olfactory bundle, which passes forward with those fibers but leaves them to pass medially beneath the putamen and the caudate nucleus and cross in the rostrum of the corpus callosum to the olfactory trigon of the opposite hemisphere, were degenerated.

4. Fibers passing posteriorly from the amputated temporal lobes into the remaining parts of the first and second temporal gyri were degenerated. The same was true, to a less marked degree, of fibers passing from the temporal lobe upward into the posterior frontal and parietal areas and backward into the occipital region.

5 and 6. Two large groups of degenerated fibers passed together upward and backward from the temporal lobes, one to the posterior part of the cingulum and the other through the posterior part of the corpus callosum to the opposite cerebral hemisphere.

7. The anterior commisure was completely degenerated except for the minute ventral component which passes to the olfactory tracts. It is our belief that, though some of this large bundle of fibers may pass to the amygdala, much of it constitutes a commissural system between the temporal neocortex of the two hemispheres. A similar conclusion was reached by Rundles and Papez (Fiber

and Cellular Degeneration Following Temporal Lobectomy in the Monkey, *J. Comp. Neurol.* **68**:267-296, 1938).

8. A small ventral part of the corticotectal system passing from the peristriate area (field 19 of Brodmann) to the superior colliculus was damaged and degenerated.

9. A rather large tract terminating in the substantia nigra was degenerated. It apparently arose from the temporal neocortex, although a partial origin from the putamen and caudate nucleus cannot be excluded on the basis of our material.

10. A large bundle terminating in the posterior part of the pulvinar and apparently arising from the region of the amygdala, known as the temporopulvinar or Arnold's bundle, was completely degenerated.

11. As noted previously, the hippocampal formation was extensively removed. As a result, at least three fifths of the fornix was degenerated. Most of these degenerated fibers end in the septal area, although a not inconsiderable minority continue ventrally into the medial mamillary nuclei.

12. That portion of the tail of the caudate nucleus lying in the temporal lobe was extirpated. As a result, the stria terminalis, which continues dorsally and then forward with the remainder of the caudate nucleus, was partially degenerated.

13. In the visual system, a small portion of the most ventral fibers of the visual radiation was interrupted on the left side. There was a corresponding small area of retrograde degeneration in the ventrolateral horn of the lateral geniculate body. The lesion on the right side was somewhat more extensive. From the anatomic evidence, as judged by Poliak's observations (The Main Afferent Fiber Systems of the Cerebral Cortex in Primates, Berkeley, Calif., University of California Press, 1932) it appears that the left homonymous upper quadrants and the upper half of the right temporal crescent were blind.

The interruption of the visual radiations produces a significant alteration in the calcarine cortex (field 17), which was first observed by Rundles and Papez (*J. Comp. Neurol.* **68**:267-296, 1938). As a result of this deafferentiation, layer IV c of this cortex becomes markedly condensed.

14. In the auditory system, the posterior tips of the medial geniculate bodies show retrograde cellular degeneration. This, according to Walker (The Projection of the Medial Geniculate Body to the Cerebral Cortex in the Macaque Monkey, *J. Anat.* **71**:319-331, 1937), indicates damage to the most anterior part of the primary auditory cortex on the dorsal surface of the first temporal convolution within the sylvian fissure.

15. In the thalamus, retrograde cellular degeneration was present in a small ventral part of the inferior nucleus of the pulvinar on the left side, and on the right side the posterior half of this nucleus was involved. In addition, the posterior tips of the medial and lateral nuclei of the pulvinar were degenerated.

16. In addition to the removal of the tail of the caudate nucleus already mentioned, a very small posteroventral part of the putamen was damaged.

17. No evidence of any degeneration in a temporopontile bundle could be found.

It is extraordinarily appropriate that this subject should be presented to the Chicago Neurological Society. Just over half a century ago Sanger Brown, one of the founders and the first president of the society in 1898, in conjunction with E. A. Schäfer, professor of physiology in University College, London, removed both temporal lobes from a rhesus monkey (animal no. VI). They noted the following operative changes (An Investigation into the Functions of the Occipital and Temporal Lobes of the Monkey's Brain, *Phil. Tr. Roy. Soc., London, s.B* **179**:303-327, 1888):

"A remarkable change is . . . manifested in the disposition of the Monkey. Prior to the operations he was very wild and even fierce, assaulting any person who teased or tried to handle him. Now he voluntarily approaches all persons indifferently, allows himself to be handled, or even to be teased or slapped,

without making any attempt at retaliation or endeavoring to escape. His memory and intelligence seem deficient. He gives evidence of hearing, seeing, and of the possession of his senses generally, but it is clear that he no longer clearly understands the meaning of the sounds, sights, and other impressions that reach him. Every object with which he comes in contact, even those with which he was previously most familiar, appears strange and is investigated with curiosity. Everything he endeavors to feel, taste and smell, and to examine carefully from every point of view. This is the case not only with inanimate objects, but also with persons and with his fellow Monkeys. And even after having examined an object in this way with the utmost care and deliberation, he will, on again coming across the same object accidentally even a few minutes afterwards, go through exactly the same process, as if he had entirely forgotten his previous experiments."

Similar alterations of behavior were observed in another rhesus monkey (no. XII) in which only the superior temporal gyri were removed on both sides.

There is no doubt that the symptoms we have observed, notably the picture of "psychic blindness," the oral tendencies, the "hypermetamorphosis" and the profound changes in emotional behavior, were observed by Sanger Brown and Schäfer in their 2 monkeys.

Unfortunately, however, they were not impressed by these observations and carried them no further. In fact, they did nothing toward elucidating the mechanisms involved in the behavior they observed. Of course, half a century ago adequate technics for analyzing animal behavior were not available. Our analysis of the alterations in behavior following bilateral temporal lobectomy clearly indicates that the changes in behavior cannot be dismissed by interpreting them as the result of a loss of "memory" and "intelligence" or as a "mental condition resembling that of an idiot," as Brown and Schäfer did. Nevertheless, it is truly remarkable how accurately the observations of the behavior of these 2 animals agree with ours, and that in the ensuing fifty years no one has recorded similar observations.

Brown and Schäfer were primarily concerned with the cerebral localization of the special senses, and as there was no loss of hearing, smell, taste or other senses in these cases, they dismissed the first case with the remark: "On localisation of functions the experiment throws no direct light; what evidence there is being entirely negative." In the second case they attributed the changes to the nature of the operation, saying that "a very great amount of vascular disturbance was . . . produced, and this must have affected, for a time at least, other portions of the brain."

The cortex of the temporal lobe is unique, and it is not surprising that its removal gives rise to unique and profound alterations. The temporal neocortex (the auditory koniocortex excluded) is the only portion of the cerebral cortex that receives very few, if any, afferent impulses from the thalamus (Walker, A. E.: *J. Anat.* **71**:319-331, 1937) and thus receives no information directly from the periphery, but only such as is relayed to it from other cortical areas. Furthermore, its efferent connections are also primarily with other cortical areas. In the instance reported here there were no demonstrable degenerated efferent tracts except those to the other areas of the cerebral cortex, the diencephalon and the upper portion of the mesencephalon (corticotectal and corticonigral tracts). Of all the areas of the cortex, the temporal is anatomically the one to which the term "association area" is most suited.

DISCUSSION

DR. PERCIVAL BAILEY: I wish to ask if the extirpation of both temporal lobes was made approximately along the same line. Here only one side was shown.

DR. PETER BASSOE: I wish to ask about the sense of smell, in view of the fact that the olfactory bulb seemed to be affected.

DR. PAUL C. BUCY: I appreciate Dr. Bailey's having raised the important question of the similarity of the extent of the extirpation and of the degeneration on the two sides. We were fortunate in this animal in that the two lesions were practically symmetric. The only significant differences, and they were slight, were somewhat more extensive destruction of the ventral fibers of the visual radiation, with a resultant larger area of retrograde degeneration in the ventrolateral part of the lateral geniculate body in the right hemisphere, and a slightly more extensive area of retrograde degeneration in the posterior part of the inferior nucleus of the pulvinar, also on the right side.

In reply to Dr. Bassoe: The olfactory bulbs, tracts and trigons were not damaged. The amygdala and hippocampal formations were removed. There was no evidence from our observations that olfactory sensation was impaired. I think Dr. Klüver might like to comment further on this point.

DR. H. KLÜVER: In view of the extensive damage to the olfactory system, it is of interest that after the operations the animal suddenly started "smelling" every object. If a nail and a piece of food are presented alternately in a large number of trials, the normal monkey in general ignores the nail and merely takes the food, whereas monkeys with the temporal lobes removed may take the nail as well as the food in hundreds of trials and each time make an olfactory examination of the object. However, if the olfactory tracts are cut in addition to removing both temporal lobes, "smelling," at least the characteristic gesture of holding the object before the nostrils, does not appear, although oral tendencies are present. The appearance of oral tendencies is, therefore, not dependent on the intactness of the olfactory system.

Experimental and Clinical Observations on the Syndrome of Obstruction of the Pineal Gland. DR. JOHN MARTIN.

The most striking feature of the available literature concerned with the function of the pineal gland is the fact that it is voluminous, confusing and unconvincing. Anatomic research has so far outstripped physiologic study in completeness and accuracy, but the full significance of the function of the pineal gland cannot be gained by anatomic knowledge alone. The present day physiologic experimentation includes extirpation of the pineal gland, feeding of pineal substance and extract and transplantation of the organ. Extracts are also being used, perhaps most widely in Germany, in opotherapy. The results of tumors of the pineal gland have led clinicians into a state of doubt and speculation.

Extirpation experiments which my colleagues and I have carried out on rats, cats, dogs and monkeys have led us to postulate the possible influence of the pineal gland on sexual and somatic maturation. Both sexual and somatic precocity have been attained in cats and dogs; somatic precocity was shown to a less marked degree in rats, and 3 immature monkeys, still under observation, have shown no significant changes. The gland was removed by open operation in all animals except the cat, and in that animal the Horsley-Clarke stereotaxic apparatus was used with good results. These changes in maturation were most noted in the male animals, but the female cats showed various changes in reproductive characteristics, even though the sexual and bodily development did not vary in the animals with lesions. All reported data have been verified by histologic study. At present a colony of second generation cats are under observation.

In a recent detailed study of the 18 cases of pineal tumor in the files of the Cushing Tumor Registry at New Haven, Conn., what might be called "the typical pineal syndrome" was found to occur in almost every instance. Five boys, all under the age of 12 years, were found to have definite signs of moderate to marked precocity, either sexual or somatic or both. This series is a source of entirely reliable data, for the histories were all carefully recorded in detail and the autopsy and operative specimens may be studied together with the case histories. It is difficult to separate the symptoms of purely pineal involvement from those of destruction of the midbrain in these cases, so that one must interpret with caution the symptoms which might lead one to ascribe certain changes to destruction

either of the pineal gland or of the diencephalon. The changes produced by a pineal tumor early, before there are any secondary destructive changes in the surrounding brain, would offer the only reliable information on the function of the pineal gland in man.

It is believed that the eventual elucidation of the function of the pineal gland will come primarily through animal experimentation, to be corroborated, if possible, by data from the clinic.

DISCUSSION

DR. VICTOR E. GONDA: I wish to ask if the pineal gland ever becomes calcified in animals, and whether Dr. Martin knows of any cases in which it was calcified in young children showing signs of mongolian idiocy. I am asking because I have under observation at this time a child aged 4, with the appearance of definite mongolism, who does not show signs of idiocy.

DR. RICHARD U. LIGHT: Has Dr. Martin any data on the development of precocious puberty in human beings from destruction of the pineal gland due to abscess?

DR. PERCIVAL BAILEY: This is an interesting attempt to adapt the Horsley-Clarke technic to the solution of this controversial problem. I wonder how accurately Dr. Martin has been able to strike the pineal body, the stereotaxic instrument not having been constructed for kittens. It seems difficult to me to remove the pineal body or destroy it in situ without disturbing seriously the venous drainage of the central part of the brain, since the vein of Galen passes in the immediate vicinity. I wonder, also, what became of the animals in which the pineal body was missed. It seems that they would be better controls than the normal litter mates, especially since the main controversy concerns the possibility that the syndrome of precocious puberty may be neurogenic rather than hormonal.

Although I agree with Dr. Martin that the problem is likely to be settled in the experimental laboratory, the pathologic changes in human beings cannot be ignored. There are several cases, described by competent pathologists, of tumors which lay in the hypothalamic region and did not involve the pineal body, yet were accompanied by precocious puberty, and others of tumors of the pineal body in early childhood of exactly the same nature and destructiveness as those Dr. Martin described which had not caused precocious puberty. I shall await with interest the histologic controls of Dr. Martin's animals.

DR. L. J. MEDUNA: The pineal gland is not developed in the newborn child. Its evolution begins at the third month of extrauterine life and is not complete until the seventh year of the child's life. Former investigations disregarded this long evolutional period. However, it makes a great difference whether the extirpation of the pineal gland—experimentally or pathologically—happens before, during or after the evolutional period of the gland. These circumstances are the cause of the contradictory results of various authors.

DR. MILTON GOLDBERG, Manteno, Ill.: I wish to ask Dr. Martin whether in these animal experiments he noted any changes in the thymus associated with the destruction of the pineal gland. I think Rowntree and his co-workers have pointed out a negative correlation between the thymus and the pineal gland.

DR. JOHN MARTIN: Most of the questions asked have already been answered in a more complete report (Davis, L., and Martin, J.: Results of Removal of Pineal Gland in Young Mammals, ARCH. NEUROL. & PSYCHIAT. **43**:23-45 [Jan.] 1940). I have not found calcification in the pineal gland of any old or young cat in my series. I have no data on the result of the destruction of the pineal gland by abscess. I have not seen any histologic differences between the thymus glands of the lesion and those of the control animals. I have, of course, failed to destroy completely the pineal gland in some animals with the Horsley-Clarke instrument; in fact, any number of animals were found to be incompletely pinealectomized early in this study, when I was first applying the instrument to destruction of the pineal body. Naturally, this report does not include data on any animals thus found to have incomplete lesions, and all the material contained in this report has been substantiated by autopsy and histologic studies, except for the

animals which are still under observation. The histologic studies are not complete because the problem is not yet entirely solved, but all the histologic observations will eventually be reported. The present paper was not intended to be a histologic report. The advantage of the use of the Horsley-Clarke instrument is apparent, for in employing it to destroy the pineal gland no part of the brain is injured except the splenium of the corpus callosum, through which the small electrode must pass to reach the gland.

Myelographic Diagnosis of Intramedullary Tumors of the Spinal Cord. Dr. A. Earl Walker, Dr. Charles M. Jessico and Dr. A. W. Marcovich.

The differential diagnosis of intramedullary and extramedullary tumors of the spinal cord is difficult or impossible, especially in the early stages. The series of intramedullary tumors of the spinal cord seen at the University of Chicago Clinics was reviewed in the hope that an accurate diagnosis might be made on the basis of the myelographic findings. In 6 cases, verified by operation, myelography by use of iodized poppyseed oil has been used as a diagnostic aid. The prime characteristic is a partial block, with lateral displacement of the oil, so that it streaks along the pedicles of the vertebrae. A second feature is the presence of a small triangular protrusion from the streak between adjacent pedicles, due to the filling of the nerve sheath with the iodized oil. To be pathognomonic of tumefaction of the spinal cord, the laterally displaced, beaded columns of poppyseed oil must maintain this position for several segments. Other types of tumor occasionally produce myelograms showing a caplike obstruction with thinning lateral streaks of iodized oil, which, however, do not extend up or down more than one segment.

This differentiation of intramedullary from extramedullary tumors is possible because of several factors: Whereas extramedullary tumors usually extend only a short distance, intramedullary gliomas tend to grow for a considerable distance within the cord. The dilatation of the cord frequently does not occlude the subarachnoid space along the entire extent of the tumor. Hence the iodized oil streaks along the lateral margins of the dilated cord for several segments and fills out the nerve sheaths at each segment.

DISCUSSION

Dr. Victor E. Gonda: I wish to ask the amount of iodized poppyseed oil injected in the case of the first stenographer.

Dr. Charles M. Jessico: In reply to Dr. Gonda, 2 cc. of iodized poppyseed oil was injected by the lumbar route, but this was found to be subdural; 1 cc. was then injected into the cisterna magna.

Neuropathologic Study of Six Cases of Psychoses in Which Metrazol Was Used. Dr. Arthur Weil and Dr. Erich Liebert.

This article appears in full in this issue, page 1031.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Gilbert Horrax, M.D., *in the Chair*

Regular Meeting, May 16, 1940

Effect of Autonomic Drugs on the Cerebrospinal Fluid Pressure in Cases of Schizophrenic and Nonschizophrenic Psychoses: I. Effect of Histamine. Dr. Emerick Friedman, Waltham, Mass.

In view of the meager information derived from routine studies of the cerebrospinal fluid in cases of the so-called functional psychoses, a relatively simple procedure has been added to the usual methods in order to obtain more knowledge

regarding the physiologic substratum of these psychoses. The procedure was as follows: After the usual pressure determinations were made, two 5.0 cc. amounts of cerebrospinal fluid were withdrawn and the resulting pressures were noted. Then, 1.0 mg. of histamine phosphate was administered subcutaneously. Cerebrospinal fluid pressures were then noted, usually at five and ten minute intervals. Two more 5.0 cc. amounts were withdrawn and the resulting pressures noted. From these readings direct prehistamine and posthistamine values were graphically displayed. Prehistamine and posthistamine Ayala indexes likewise were plotted. These values were compared with those determined for control subjects to whom histamine was not given. In addition, 20 schizophrenic and 20 nonschizophrenic patients were given histamine after withdrawal of 20 cc. of cerebrospinal fluid and the resulting pressures recorded at three minute intervals. In the last group of experiments the average curve for nonschizophrenic subjects was of decidedly greater amplitude than that for the schizophrenic subjects.

The comparative effect of histamine on the cerebrospinal fluid pressure was studied by means of this procedure in 57 nonschizophrenic and 64 schizophrenic patients. Grossly, the average reaction of the cerebrospinal fluid pressure of the nonschizophrenic patients to histamine was practically twice that of the schizophrenic patients. That this was a proportionate rise is shown by the parallel responses in the Ayala indexes under the influence of histamine. Expressed in figures, 72 per cent of the nonschizophrenic and only 45 per cent of the schizophrenic patients showed a rise in the cerebrospinal fluid pressure of 30 mm. or more in response to histamine; 7 per cent of the nonschizophrenic and 23 per cent of the schizophrenic patients showed a fall. The average direct responses to histamine in the nonschizophrenic patients were 38.9 mm. in five minutes and 42.3 mm. in ten minutes after injection; in the schizophrenic patients the rises were respectively, 6.1 and 19.2 mm. The average distortions of the Ayala index due to histamine were 2.2 for the nonschizophrenic and 0.9 for the schizophrenic patients.

Although the number of cases of psychotic subtypes in this study were insufficient for statistical analysis, patients with alcoholic and syphilitic psychoses, as well as those having psychoses associated with imbecility, showed a substantial and sustained or progressive rise in cerebrospinal pressure. On the other hand, the average response of the "organic-hyperkinetic" group to histamine was remarkably low, resembling that of the schizophrenic group.

DISCUSSION

DR. WILLIAM G. LENNOX: This is an interesting presentation. I am disappointed that Dr. Friedman did not use the intravenous route, because the effect is so much more clearcut—within fifteen or twenty seconds after the injection there is a perpendicular rise of cerebrospinal fluid pressure, which then falls slowly to the neighborhood of the previous level. Mrs. Gibbs and I, working with Dr. Weiss, observed that after the injection of histamine the blood leaving the brain was much more concentrated than the arterial blood, indicating that in passage through the brain the blood had lost fluid. I wonder, therefore, whether the increased cerebrospinal fluid pressure after injection of histamine was due to the passage of fluid into the brain or to the dilatation of cerebral arterioles, which is known to occur. Were headaches obtained with this method of injection? It would be interesting to know whether schizophrenic persons behave similarly to normal persons in that respect. In general, it seems to me that the author's observations agree with those which Thompson and others have made showing that schizophrenic patients seem to react much less promptly than normal persons to various physiologic stimuli, such as high carbon dioxide tension.

DR. EMERICK FRIEDMAN, Waltham, Mass.: I thank Dr. Lennox for his remarks. I did not use histamine intravenously because the patients were a mixed group, included among whom were some rather old arteriosclerotic persons, and I was afraid of possible unfavorable reactions. It is known from the usual gastric analysis that subcutaneous use of histamine is without danger. I do not think that I can add anything to what Dr. Lennox has said in regard to cerebral edema

or increase in fluid from the vessels. However, I can say that there was no greater increase in incidence of headaches due to histamine than of headaches usually encountered after lumbar puncture in state hospital practice.

The Babinski Sign: Influence of Exertion and of Locomotion on the Plantar Reflex in Normal and in Mentally Defective Persons. Dr. Paul I. Yakovlev and Dr. Malcolm J. Farrell, Waverly, Mass.

In the summer of 1939, one of us examined the plantar reflex in a group of 168 college undergraduates in a Reserve Officers' Training Camp before and after a forced march of 14 miles (22.4 kilometers), during military maneuvers. In 12, or 7.2 per cent, of these 168 young men a Babinski sign developed after the march. In 10 a Babinski sign appeared unilaterally and in 2 bilaterally.

A relative measure of the effect of exertion on the plantar reflex in a group of normal persons having been obtained, we examined the plantar reflex before and after seven hours of ordinary work in a group of 229 adult "imbeciles" at a farm colony connected with the Walter E. Fernald State School. The work consisted of sawing, splitting and stacking cordwood in the woodyard. Of 229 mentally defective persons thus examined, a Babinski sign developed in 49, or 21.4 per cent. In 13 of the cases in which the sign was positive, or in 5.7 per cent, it was bilateral; in 24, or 10.5 per cent, it was unilateral, and in 12 cases, or 5.2 per cent, a tendency to a Babinski sign occurred, in 11 of them unilaterally.

Exertion in the form of a march, i. e., progressive locomotion, was particularly effective in causing the development of the Babinski sign. Thus, in a group of 60 young "imbeciles" selected among those in whom after a day of ordinary work in the woodyard the plantar reflex remained flexor, a Babinski sign developed in 13 per cent after a march of 10 miles (16 kilometers) and in 23 per cent after a march of an additional 14 miles (22.4 kilometers).

Of the other signs of the so-called pyramidal series, a record was made only of the "fan sign." This sign developed in 2.2 per cent of persons after a day of ordinary work and in 10 per cent after a march of 24 miles (38.4 kilometers).

Among other effects of exertion, the following were noteworthy: The threshold of the plantar reflex was higher after exertion, and the response of the big toe often became sluggish and hesitant. Circulatory disturbances of the extremities, consisting of cyanosis, hyperhidrosis and a fall of cutaneous temperature of the feet and toes, were conspicuous. However, the outstanding feature noted after exertion was an extraordinary increase in "paratonic" rigidity. This consisted of involuntary anticipation of and compulsive resistance to passive movements, resulting in utter inability to relax an extremity or part of it under examination, in spite of manifest good will to do so.

Some of the factors influencing the behavior of the plantar reflex after exertion were accessible to appraisal. 1. The chronologic age had a distinct influence on the occurrence of the Babinski sign after exertion. The group of mentally defective persons were from 8 to 10 years older than the group of students in the military training camp, and the mental defectives in whom a Babinski sign developed after exertion were 4 years older (average age, 35) than those in whom the response could not be elicited (average age, 31).

2. The factors of premature birth, birth injury, infantile convulsions and acute diseases of the nervous system in infancy or early childhood, occurring singly or in combination, were recorded in 68 per cent of the mentally defective persons in whom a Babinski sign developed and in 44 per cent of the mentally defective persons who showed no change in the plantar reflex. It is noteworthy that the inborn and prenatal factors, such as premature birth and convulsive diathesis, were more prevalent than the postnatal and acquired factors, and were twice as frequent in the histories of persons with a positive Babinski sign as in those of persons with a negative response.

3. The age of establishment of upright locomotion and of articulate speech revealed a characteristic and significant relation to the occurrence of a Babinski

sign after exertion. The group of 109 mentally defective persons who showed no change in the plantar reflex after exertion walked on the average at the age of 2 years, or one year later, and talked at the age of 2½ years, or one and a half years later, than the average normal person. However, the group of 34 mentally defective persons in whom a Babinski sign developed walked at the age of 2½ years, or one and a half years later, and talked at the age of 3½, or two and a half years later, than the average normal persons.

These correlations show that the occurrence of a Babinski sign after exertion is largely conditioned by the past development of the cerebral functions.

In conclusion, it is legitimate to ask what may be the physiologic implications of these observations. The observations presented indicate, we believe, that the occurrence of a Babinski sign under the influence of exertion, especially progressive locomotion, reveals a state of functional deficiency in the motor cortex, specifically in area 4 of Brodmann. However, the occurrence of a "fan sign" shows that the cortical deficit induced by exertion is not restricted to that area alone, but is potentially more generalized, and involves the more anteriorly situated premotor area 6 as well. The increase, after exertion, of autonomic disturbances, such as cyanosis, sweating and lowering of the temperature of the extremities, also points to functional upsets in the premotor cortex. This contention is further supported by the characteristic increase, after exertion, of "paratonic" rigidity. In the light of recent experimental evidence we are inclined to assimilate the "paratonic" rigidity and associated motor disturbances of mentally defective and demented persons with the changing spasticity, forced grasping, resistance to passive manipulation and "retardation of motor adjustments" described by Fulton and his co-workers in monkeys after bilateral ablation of the premotor cortex. In connection with this, it becomes interesting to compare the aimless agitation and indiscriminate gluttony, notoriously characteristic of many feebleminded and demented persons, with the greatly increased "spontaneous motor activity and associated ravenous appetite" shown by monkeys after removal of the frontal lobes proper. The observations presented invite the inference that it is essentially the frontal lobes that bear the brunt of the effects of exertion on the nervous system, and so reveal their primary deficiency in the feebleminded by a significantly frequent and characteristic occurrence of the Babinski sign, the "fan sign," autonomic disturbances and "paratonic" rigidity after relatively moderate exertion.

The "weakness of mind" in the feebleminded is essentially a weakness of "dominance" which the cerebral cortex has achieved in man over the integrative functions of the nervous system.

DISCUSSION

DR. H. HOUSTON MERRITT: I wish to compliment Dr. Yakovlev on this thorough study. Much work and time were put into it in an effort to show that in these mentally defective persons there is something organically wrong with the brain. Evidence of this defectiveness can be brought out by exertion of the kind described here.

DR. WILLIAM G. LENNOX: Do the Babinski responses obtained in the normal subjects indicate that they also are defective?

DR. PAUL I. YAKOVLEV, Waverly, Mass.: There is no relation between intelligence and the behavior of the plantar reflex. Under an exertion sufficiently severe even a healthy and vigorous person may "turn his toes up."

DR. WILLIAM G. LENNOX: I wonder if abnormal reflexes were confined to the legs. Could a positive Hoffmann sign be obtained?

DR. PAUL I. YAKOVLEV, Waverly, Mass.: We did not look for the Hoffmann sign.

Book Reviews

Explorations in Personality: A Clinical and Experimental Study of Fifty Men of College Age, by Workers at the Harvard Psychological Clinic. Henry A. Murray, M.D., Ph.D., Editor. Price, $8.50. Pp. 761. New York: Oxford University Press, 1938.

"This Book is Gratefully Dedicated by its authors to Morton Prince, who had the vision, raised the endowment and was the first director of the Harvard Clinic, to Sigmund Freud, whose genius contributed the most fruitful working hypotheses, to Lawrence J. Henderson, whose expositions of scientific procedure established a methodological standard, to Alfred N. Whitehead, whose philosophy or organism supplied the necessary underlying generalities, and to Carl G. Jung, whose writings were a hive of great suggestiveness."

The reader may well speculate as to the writhings of these bedfellows and wonder why certain other deities were left out! Nevertheless, the list reveals the author's bent and his eclecticism. His theme is that psychology should not lose sight of human nature as it operates in everyday existence; his belief is that progress can be made by conscientious clinical research and by seeking experimental evidence for the validity of certain general intuitions about human nature. "Personology" is the name Murray gives to this branch of psychology, and he realizes fully that it "is still in diapers, enjoying random movements." In the beginnings of such a science exact measurements are impossible. One must choose the most probable hypotheses and test them by new methods. Most of the hypotheses chosen by Murray are freudian; his shrewd invention of methods to test them is the most important contribution of the book. The very fact that the hypotheses are recognized as such and are subjeced to test is important, for psychoanalysts are too prone to accept them as proved "facts," when the evidence is all clinical and is so voluminous that it is never adequately presented. Murray, like Prince before him, has a flair for human psychologic experiment, and this book, as the title indicates, is the work of an explorer.

The results are important as an evaluation of freudian theories by new methods. Starting with the opinion that today psychoanalysis provides the best orientations for the study of human personality, the experimenters concluded at the end of their investigations that seven of Freud's main hypotheses are helpful and seem to concur with their findings: (1) the theory that there are unconscious processes influencing consciousness and behavior which resemble conscious processes; (2) the hypothesis that among active unconscious processes are to be found the traces of infantile themas or similes of these themas; (3) the observation that there are certain classic infantile themas that are especially influential in determining development; (4) the concept of the sexual instinct, its combinations, permutations and sublimations, and the barriers that are set up against it; (5) the theory which draws attention to the eternal conflict between an individual and his culture; (6) the theory of repression and the enumeration of various modes by which repressed tendencies commonly find disguised expression, and (7) the concepts of projection and rationalization.

In criticism of the freudian system, some of the points chosen by Murray are: (1) the confusion of fact and theory; (2) the distorting effect of pansexualism; (3) the neglect of the muscles, arms and legs and the necessities and pleasure of locomotion and the manipulation of objects (freudian psychology is limited to the torso); (4) the absence of concepts to account for ego structuration and the pleasures of will and self mastery (freudian theories do not recognize the fact that fear is more shameful than lust or aggression); (5) the conceptualization of fear merely as an affect, rather than as an instinctual tendency on a par with sex and agression; (6) the misinterpretation or neglect of the need for inviolacy, e. g., pride, self respect and honor; (7) the disposition to oversimplify, which leads analysts to overlook many reaction systems; (8) the neglect of what the ordinary man thinks of as the major factors in his psychologic makeup: abilities and disabilities, tastes, sentiments and social attitudes, friendships affiliations, conscious interests and religious aims, and (9) the minimization of sociologic factors.

The introduction in chapter I gives in 35 pages the best discussion one can find on contemporary schools of psychology, their points of cooperation and their mutual misunderstandings. In chapter II Murray begins the exposition of his own experimental approach, and at once his style becomes wary and, unfortunately, somewhat involved. Pages of remarkably interesting and important ideas are sometimes confused by the introduction of new terms, quotations (though often apt and erudite) and parenthetic phrases. The three most important new terms seem justified and useful; they are "regnant," "press" and "need." Regnant processes are those which at the time hold sway over the personality, obviously those in the field of attention, but also those that are more emotional and less conscious. Each person has his own regnancies, which combine to mold his personal reactions, making certain "themas" run through his life story. "Press" and "need" might be looked on as the two elements of a "complex" in the psychoanalytic sense. Their separation is meaningful in that "press" indicates the environmental potentialities, whereas "need" is organized in the brain; need is a pattern (inherited or acquired) which leads the organism to attend and respond to a certain press in the environment. The endurance of a certain kind of press in conjunction with a certain kind of need defines the duration of a single episode; certain press-need combinations determine the "themas" which run through an individual person's type of reaction.

The term "trait" as used by Allport and others is not inclusive enough for Murray, who is more interested in the study of traits common to many persons; in fact, traits are needs activated by the press of the environment. Needs, however, are more than traits, for they may never become manifest in overt behavior, as a trait must, being an objective attribute of conduct. Needs are diffuse, general traits. Dynamic psychology flowered because trait psychology failed to "explain phenomena, failed to get at the root of things." Trait psychology is too much concerned with what is clearly manifest. Trait psychology can describe the concrete individuality of a human being, but dynamic psychology insists on the individuality of every episode in the life of a human being.

Murray thinks that the most important contribution to personology made by his group is the method: ". . . numerous sessions, of which as many as possible are controlled experiments, conducted by different examiners who work independently until at a final session they meet to exchange their findings and interpretations. By following this program a great deal of information is assembled which can be used to interpret the reactions of each subject in each experiment. In this way an experimenter is able to discover many of the operating variables, rather than having to content himself with crude, merely statistical results, such as are obtained in most experiments (which are performed on a large number of subjects about whose personalities nothing is known)."

This is a pioneering book, difficult but important; it is one of the first appreciative, yet objectively critical, evaluations of psychoanalysis.

Neurology. By S. A. Kinnier Wilson. Edited by A. Ninian Bruce. Price, $21. 2 vols.; pp. 1,838. Baltimore: Williams and Wilkins Company, 1940.

The eagerly awaited volumes of Kinnier Wilson's "Neurology" are now ready for distribution. It was common knowledge among neurologists that Wilson had a textbook of neurology in preparation, a work which, because of the author's reputation as a clinician, was awaited with great anticipation. Unfortunately, Wilson died before his book was published and it was felt that the results of his wide experience were lost. Fortunately, however, his work was almost completed before his death, and it now appears with text unaltered and with the arrangement of chapters as he wished them. The volumes have been edited by Dr. A. Ninian Bruce.

The arrangement of the material is unorthodox. Unlike almost all other texts of neurology, which begin peripherally and work inward, Wilson proceeds in totally different fashion, discussion of the details of which would carry one too far afield. The arrangement of material is not nearly as important, however, as the fact that his book covers all conceivable subjects pertaining to neurology. There are no apparent omissions; on the contrary, the volumes contain many subjects

not found in any other neurologic texts. In this sense, therefore, they are truly encyclopedic. Obviously, it is impossible to cover as fully as might be desirable subjects which can be treated *in extenso* only in systems of neurology. The discussion of encephalitis of toxins and poisons, for example, suffers from omissions. Despite the great scope of the book there is at times an attempt to cover too much ground, the result being brief dismissal of a subject which the author was undoubtedly capable of discussing in considerably greater detail. Nevertheless, it must be remembered that the book is a text, that it was written by a single person and that it represents wide clinical acquaintance with the problems discussed.

The work is amazing in its citation of source material and in the analysis and cataloging of this material. One cannot but admire the scholarship necessary to produce such a work, but at the same time one is aware also of an alive, critical faculty which has made it possible to fit facts in their proper places.

There are many aspects of the volumes on which one could comment. The treatment of encephalitis is excellent and the warning against too ready acceptance of the concept of acute disseminated encephalomyelitis quite timely. The short discussion of this particular problem is full of pertinent clinical facts. The description of multiple sclerosis is excellent, but the discussion of pathogenesis lags behind some of the more recent studies. The chapter on myelitis is somewhat obscure, chiefly because the subject needs much clarification. Wilson's pertinent remarks on Landry's paralysis, which he regards as a concept of dubious value, could with equal force be applied to that of myelitis. The treatment of neuritis is excellent but in some parts sketchy, and introduces a new term "plexitis" for disease of the plexuses. This tendency to substitute new terms for old is sometimes stimulating, but often results in the substitution of a term which is no clearer than the one which it replaces, for example, thrombomyelia for acute myelitis. Wilson also offers many classifications of disorders, some of which differ much from those now in vogue. Many of them are helpful, but some are unorthodox.

The chapters on neurosyphilis and the extrapyramidal disorders are excellent. In his discussion of the cerebral diplegias, Wilson reserves the term Little's disease for cases in which there is evidence of illness at birth, and confines the term cerebral diplegia to cases in which the disease appears during infancy or shortly after birth. His discussion of these conditions is clear and shows keen acquaintance with a very complicated subject. The chapter on the myopathies is clear and concise. One of the best chapters in the book is that on the epilepsies. The chapter on tumors of the brain follows closely the classification of Cushing and Bailey. The vascular diseases are well covered, and the short discussion of cerebral vascular spasm reveals Wilson at his best as a keen clinician. It should be read by physiologists and clinicians alike.

The description of symptomatology is variable. Some chapters, such as those on paralysis agitans, contain a vivid running account of the symptoms and their evolution in the course of the disorder. Others are disappointing in the sense that they constitute rather a tabulation of symptoms, without reference to the actual evolution of their development. The result is at times a sterile rather than a dynamic account of a disease process.

These two volumes of Wilson's "Neurology" stand as a monument to one of the great neurologists of our time. They are remarkable in that they represent the work of a single man who in these days of rapidly accumulating literature and constantly changing concepts was nevertheless able to select studies pertinent to the many problems discussed. They are remarkable also in that they represent for the most part the outcome of personal experience over a period of many years. In this sense they will take their place with Oppenheim's and Gower's famous texts. It is tragic that the author could not have lived to enjoy the acclaim which these volumes will undoubtedly bring. There may be some compensation, however, in the fact that they will serve to perpetuate a name already made famous in neurology for many brilliant studies. The books are recommended without qualification to neurologists and practitioners, who will find them a source of much critically digested material.